Pilot study of dual-energy (DE) contrast-enhanced (CE) digital mammography to detect breast cancer in patients with increased breast density (BI-RADS category c or d).

Study Protocol & Statistical Analysis Plan

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Comprehensive Cancer Center
University of Alabama at Birmingham
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Protocol UAB F141210004: Pilot study of dual-energy (DE) contrast-enhanced (CE) digital mammography to detect breast cancer in patients with increased breast density (BI-RADS category c or d).

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1.0 INTRODUCTION AND STUDY RATIONALE

1.1 Breast Cancer and Screening

Breast cancer is the second leading cause of cancer mortality in women, and the American Cancer Society estimates 232,670 new cases of invasive breast cancer in women in 2014 and 2360 new cases in men (1). Since 1990, the mortality rate from breast cancer has decreased more than 30% in the United States (2), and this is likely related to both the implementation of screening mammography and significant advances in the treatment of breast cancer (3). Mammography remains the standard of care for early detection of breast cancer prior to clinical symptoms, facilitating treatment of malignancy when it is more likely curable; however, this may also result in a certain amount of overtreatment (7-10). Additionally, certain women have been shown to benefit from additional screening with contrast enhanced breast (MRI) (11); therefore, a given patient's screening regimen is optimized after discussion with a health care professional regarding personal risk assessment as well as the benefit and potential harms of various imaging studies. Several randomized controlled trials and meta-analyses have shown a reduction in breast cancer mortality with general agreement of a 15 to 20% relative risk reduction in breast cancer mortality resulting from invitation to screen (12-17).

1.2 Limitations of Screening Mammography

While mammography has shown proven benefit it is not a perfect screening test, with documented limitations (18-28) including false negative rates ranging from 6 to 46% (4;29-31). Retrospective and prospective studies have shown screening breast MRI is valuable for early detection in women at increased risk for breast cancer (32-39). Breast MRI has been shown to have a higher sensitivity for detecting breast cancer (71-93.8%) when compared to mammography (19-58.8%) (33,36-40). One condition where screening might be more likely to fail is in women with dense breasts. According to the breast cancer surveillance consortium data from 1994-2009, false negative rates for mammograms categorized as heterogeneously dense or extremely dense breasts were 50.56% and 13.93% respectively as compared to exams categorized as scattered fibroglandular tissue 32.25% and almost entirely fat 3.25%.

1.3 Breast Density and Screening

Since 2009, nineteen states have enacted dense-breast legislation requiring mammography providers to notify women categorized as having dense breast tissue about their condition. There is also a bill proposed in the US House currently. There is little evidence to direct supplemental or alternative imaging evaluation in patients with dense breast tissue who are not eligible for high risk screening with contrast enhanced breast MRI. The Digital Mammography Imaging Screening Trial (DMIST) compared film mammography with digital mammography to reveal a similar accuracy between the two modalities for the general screening population (41). However, digital mammography was more accurate than film mammography in pre- or peri-menopausal women, women with dense breasts, and women under the age of 50 (42). Mean glandular dose per view averaged 2.37 mGy for film mammography and 1.86 mGy for digital mammography in DMIST (43). Breast density has been associated with decreased sensitivity of mammography 68% in dense breasts versus 85% in non-dense breasts (4).

According to the breast cancer surveillance consortium data from 1994 to 2009, approximately 38.65% of women have heterogeneously dense and 9.56% women have extremely dense breasts. Aside from the use of digital mammography little data is available to direct additional or alternative imaging evaluation in this population.

1.4 Contrast Enhanced Mammography

Contrast enhanced mammography was first described in 1985 by Watt et al. utilizing digital subtraction angiography of the breast (44,45). This technique is based on the principle of digital subtraction between two images. One of the images has morphological data and the second image has information relative to breast vascularization. Weidner et al demonstrated the hypervascularity of invasive malignant breast tumors in 1991 (46). Initial studies focused on temporal subtraction CE mammography (47-50); however, no significant difference has been shown between the kinetic enhancement patterns observed for malignant or benign breast lesions. Dual-energy CE mammography was first described in 2003 by Lewin et al as an alternative to the temporal subtraction technique (51). This technique is based on the interaction between gamma rays and iodine. A "high energy" image above the k edge of iodine (33.2 keV) is obtained to distinguish vascular structures after iodine contrast administration. A "low energy" image (below 33.2 keV) is obtained for morphological information. The digital subtraction of these images highlights the vascularized structures similar to a temporal subtraction method. This technique allows for bilateral breast imaging after a single contrast administration. Dromain et al showed that DE CE digital mammography had a higher sensitivity (93%) than mammography alone (78%) with no reduction in specificity (63%) (4). This group subsequently showed increased diagnostic performance in 6 readers with better detection of malignancy and no increase in false positives with the addition of DE CE digital mammography with or without ultrasound (3). Recently, Jochelson et al compared DE CE digital mammography with breast MRI in patients with known breast carcinoma to reveal similar levels of primary tumor detection (6). MRI detected additional ipsilateral lesions better than DE CE digital mammography (6). However, CE DE digital mammography had a higher specificity with fewer false positives (6). The positive predictive value of an enhancing lesion was higher with DE CE digital mammography than for MRI (97% vs 85%, $p<0.01$) (6). These preliminary results suggest that DE CE digital mammography may be a feasible adjunct or an alternative to routine breast screening with conventional digital mammography in certain groups such as the population with dense breasts.

2.0 OBJECTIVES

Primary:

- To determine the accuracy of DE CE mammography when compared to full field digital mammography (FFDM) in patients with increased breast density (BI-RADS category c or d breast density).

Secondary:

- To assess interobserver and intraobserver variability observed with DE CE digital mammography as compared to FFDM. We hypothesize that DE CE digital

mammography assessment will have less interobserver and intraobserver variability than FFDM.

- To evaluate any breast cancer identified by each modality including pathologic diagnosis, histologic grade, tumor size, receptor profile, axillary nodal status, and distant metastases.

- To determine through questionnaires and study screening assessments whether DE CE digital mammography has associated factors that make it a less desirable patient experience than FFDM, and determine the acceptability of a randomized screening trial to compare the two modalities.

3.0 STUDY DESIGN OVERVIEW

3.1 Study Design

The proposed prospective pilot study will invite women meeting eligibility criteria to undergo screening digital mammography and DE CE digital mammography. This trial is unique because to our knowledge this technology has not been assessed in women with BI-RADS category c and d dense breasts as an adjunct to routine screening. We will determine the potential of this imaging technique as an alternative or adjunct to screening mammography in this patient population. Patients will undergo bilateral digital mammography with 4 views and DE CE digital mammography.

We hypothesize that DE CE digital mammography will have improved diagnostic accuracy when compared to FFDM in patients with increased breast density. Sensitivity, specificity, positive predictive values (PPV1 and 3), negative predictive value (NPV), call back rate, false negative rate, and accuracy will be assessed.

This imaging technique is hypothesized to improve detection of masses (particularly those that enhance post contrast administration) in patients with dense breasts; thereby decreasing the false negative rate. Additionally, the ability of this technique to demonstrate contrast enhancement of masses may decrease call back rate as compared with FFDM. This trial is unique because to our knowledge this technology has not been assessed in this group of patients and this study will provide data to prepare for a larger clinical trial to determine the accuracy of this novel imaging technique as an alternative or adjunct to screening mammography in this patient population.

Figure 1 – Study Design

SCHEMA

Patient with heterogeneously or extremely dense breasts meeting eligibility criteria consented for study.

↓

FFDM and DE-CE Mammography performed

↓

Truth determined by pathology diagnosis or one year follow-up.

3.2 Endpoints

Primary:

- Sensitivity, specificity, positive predictive values (PPV1 and 3), negative predictive value (NPV), call back rate, false negative rate, and accuracy will be assessed.

Secondary:

- Each study will be interpreted by 4 radiologists with varying levels of experience blinded to results with separation of time. Interobserver variability will be assessed utilizing raw data agreement and Kappa coefficient.

3.3 Study Duration and Dates

Two years.

3.4 Safety and Efficacy Monitoring

This prospective pilot study will be approved by the UAB Institutional Review Board with a data safety monitoring plan approved by the UAB CCTS. In addition, approval by the UAB Radiation Safety Committee is necessary since patients who participate will be undergoing additional radiation associated with the DE CE digital mammographic study. The estimated dose from the combined low and high energy levels for DE CE is reported as 1.2 times that delivered during a routine single mammographic view (53). Imaging will be performed on GE Senographe DS and Essential mammography units with software upgrades for DE CE digital mammography. The UAB breast imaging section is an ACR accredited Breast Center of Excellence with mammography equipment certification by the FDA and ACR. The device under investigation is considered a non-significant risk device per the 21 CFR 812.3 definition 1) it is not intended as an implant; 2) is not purported or represented to be for a use in supporting or sustaining human life; 3) is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health; 4) and it does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject." Non-significant risk devices do not require a formal Investigation Device Exemption.

3.5 Ethical Considerations

This study will be conducted in accordance with Good Clinical Practice, the Declaration of Helsinki, and 21CFRPart50 – Protection of Human Patients, Part 56 – Institutional Review Boards, and the other applicable local ethical and legal requirements.

The Ethics Review Committee/Institutional Review Board (IRB) must be constituted according to Code of Federal Regulations (CFR).

The IRB must be informed by the principal Investigator of all subsequent protocol amendments and of serious or unexpected AEs occurring during the study which are likely to affect the safety of the patients or the conduct of the study. Approval for such

changes must be transmitted in writing to the Sponsor (UAB) via the Principal Investigator.

The Principal Investigator or designee will notify the IRBs and investigators when the study is placed on "hold", completed, or closed to further patient enrollment.

3.6 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki will be implemented in this study. A written informed consent will be obtained in accordance with 21CFR50.25 and 21CFR50.27 before the protocol – specified procedures are carried out. Patients, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

The consent form generated by the Principal Investigator must be approved (along with the protocol) by the applicable IRB. Consent forms must be in a language fully comprehensible to the prospective patient. The consent form should be signed and dated by the patient or the patient's legally authorized representative, and the investigator. Each patient's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and sponsor (UAB).

3.7 Confidentiality

Patient names will not be supplied in the data. Only the patient number and patient initials will be recorded in the CRF, and if the patient name appears on any other document (e.g., laboratory report), it must be obliterated. Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be informed that representative of the independent IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

4.0 SELECTION OF PATIENTS

4.1 Number of Patients

Approximately 200 patients should be enrolled in this study. It is planned to recruit this sample in one center.

4.2 Inclusion Criteria

Patients meeting all the following criteria will be considered for enrollment into the study:

1.Have heterogeneously or extremely dense breasts (BI-RADS category c or d).
2. Have GFR >60.
3. Are 19 years of age or greater.
4. Signed informed consent.

4.3 Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Have a history of iodinated contrast allergy.
2. Are pregnant or lactating as determined by routine standard practice.
3. Have a personal history of breast cancer;
4. Have a history of prior breast excisional biopsy. (Patients with a history of core needle biopsy will not be excluded).
5. Have a history of prior breast reduction mammoplasty surgery.
6. Have a history of prior breast augmentation surgery.
7. Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.

4.4 Patients of Reproductive Potential

The patient must not be pregnant or breast-feeding at enrollment in the study. The patient's will be asked if there is any possibility that they could be pregnant. Serum pregnancy tests will be obtained if there is a possibility of pregnancy as per routine breast imaging protocol.

5.0 STUDY TREATMENTS

5.1 Overall Plan

The proposed prospective pilot study will invite women meeting eligibility criteria to undergo screening digital mammography and DE CE digital mammography. This trial is unique because to our knowledge this technology has not been assessed in women with BI-RADS category c and d dense breasts as an adjunct to routine screening, and to determine potential of this imaging technique as an alternative to screening mammography in this patient population. Patients will undergo either bilateral digital mammography with 4 views or bilateral digital mammography with 4 views plus DE CE digital mammography. Dual-energy CE digital mammography will be performed with bilateral craniocaudal and mediolateral oblique views at high and low energy levels. These images will be obtained after iodinated contrast administration. Intravenous injection of iodinated contrast agent (Omnipaque 350 (iohexal, GE, Shanghai, China) at a dose of 1.5 mL per kilogram of body weight will be injected at a rate of 3mL/sec (similar dose used for computed tomography studies). Standard departmental protocols for contrast administration will be followed. Imaging will begin 2.5- 5.0 min after contrast administration. Case report forms (CRFs) will be completed for each imaging study to record technique, views, dose, breast compression force, compressed breast thickness and image time. Screening digital mammogram images will be initially read by a radiologist specialized in breast imaging with 5 to 25 years of breast imaging

experience. A different breast radiologist will read the DE CE digital mammogram with a routine screening interpretation of only the low energy views initially. Subsequently, the entire DE CE digital mammography exam will be interpreted with all images by the same reader. Readers will interpret their designated study independently blinded to the additional study and results will be documented on the CRFs. Additional clinical work up will be performed based on both studies after the initial independent reads. All lesions will be further evaluated by standard of care. Both digital mammograms and DE CE mammograms will be assessed for quality. Truth will be determined using pathologic diagnoses when available or one year negative follow-up imaging. Calculations will be performed for sensitivity, specificity, negative predictive value, positive predictive value 1 for call back (PPV1), positive predictive value 3 for biopsy performed (PPV3), cancer detection rate, false negative rate, and call back rate.
To evaluate for interobserver and intraobserver variability, all studies will be read by 2 additional radiologists blinded to truth and randomized over time to minimize memory recall. Interobserver and intraobserver variability will be assessed utilizing raw data agreement and Kappa coefficient.

6.0 STUDY PROCEDURES AND SCHEDULE

6.1 Screening Phase

Each potential patient will be examined before the start of the study to determine their eligibility for participation. The following investigation will be performed:

(1) **iSTAT creatinine to determine GFR** per standard of care.
(2) **Pregnancy Test** (if indicated) – within 1 day of mammography per routine protocol.

7.0 EFFICACY AND SAFETY [

7.1 Efficacy Measurements

FFDM and DE CE digital mammography efficacies will be assessed by pathologic diagnosis when appropriate or by one-year follow-up mammography.

7.2 Safety Monitoring

Safety will be monitored throughout the study by physical examinations, review of AEs.

7.2.1 Adverse Events

7.2.1.1 Definitions

7.2.1.1.1 Adverse Event Definition

An **adverse event** is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship

with the treatment. An AE can be any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

7.2.1.1.2 Serious Adverse Event Definition

A **serious adverse event** is any adverse event, occurring at any dose and regardless of causality that:

- Results in **death**.
- Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction which hypothetically might have caused death had it occurred, ie, it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient **hospitalization or prolongation of existing hospitalization.** Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (eg, surgery performed earlier than planned).
- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a person' ability to conduct normal life functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clarification should be made between the terms "serious" and "severe" since they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as "serious", which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.2.1.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient and/or in response to an open question form study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate page of the CRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the appropriate pages of the CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

All SAEs that occur during the course of the study, as defined by the protocol, must be reported by the investigator to the Principal Investigator or Designee at the UAB Clinical Study Unit by faxing (FAX: (205) 975-2963) the SAE Form **withing1 working day** from the point in time when the investigator become aware of the SAE. In addition, all SAEs including all deaths, which occur up to and including 30 days after administration of the last dose of treatment must be reported to the Principal Investigator or Designee at the UAB clinical Study Unit within 1 working day. All SAEs and deaths must be reported whether or not considered causally related to the study treatment.

The SAE form, which is a component of the CRF, will be provided to each clinical trial site. The information collected includes a minimum of the following: patient identification number, a narrative description of the event and an assessment by the investigator as to the intensity of the

event and relatedness to the study treatment. Follow-up information on the SAE may be regulated by the Principal Investigator or Designee.

If there are serious, unexpected adverse drug reactions associated with the study treatment the Principal Investigator or Designee will notify the appropriate regulatory agency(ies) and all participating investigators on an expedited basis. It is the responsibility of the investigators to promptly notify the IRB of all unexpected serous adverse drug reactions involving risk to human patients.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial or before study drug was given, are not to be considered AEs unless they occur at a time other than the planned date.

For both serious and non-serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

Intensity for each AE will be determined by using the NCI CTC, Version 3.0 as a guideline, wherever possible. The criteria are provided in Appendix B. In those cases where the NCI CTC criteria do not apply, intensity should be defined according to the following criteria:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with normal daily activities.
Severe	Inability to perform normal daily activities.
Life Threatening	Immediate risk of death from the reaction as it occurred.

For grading of abnormal laboratory AEs (grades 1-4), please se the NCICTC in Appendix B.

Relationship to the study treatment will be determined as follows:

None	No relationship between the experience and the administration of study treatment; related to other etiologies such as concomitant medications or patient's clinical state.
Unlikely	The current state of knowledge indicates that a relationship is unlikely.

Possible	A reaction that follows a plausible temporal sequence from administration of the study treatment and follows a known response pattern to the suspected study treatment. The reaction might have been produced by the patient's clinical state or other modes of therapy administered to the patient.
Probable	A reaction that follows a plausible temporal sequence from administration of the study treatment and follows a known response pattern to the suspected study treatment. The reaction cannot be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy at follows a plausible temporal sequence from administration of the study treatment and follows a known response pattern to the suspected study treatment and can be confirmed with a positive re-challenge test or support laboratory data.
Definite	A reaction that follows a plausible temporal sequence from administration of the study treatment and follows a known response pattern to the suspected study treatment and can be confirmed with a positive re-challenge test or supporting laboratory data.

Monitoring of Adverse Events and Period of Observation

Adverse events, both serious and non-serious, and deaths will be recorded on the CRFs up to 30 days after administration of the last dose of study treatment. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Any SAE that occurs at any time after completion of study and the designated Follow-up Period, which the investigator considers to be related to study medication, must be reported to the Principal Investigator or Designee at the UAB Clinical Study Unit.

Procedures for Reporting Pregnancy Exposure and Birth Events

If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must inform her treating physician immediately and discontinue treatment. The Principal Investigator or Designee must also be contacted immediately. The pregnancy must be followed through delivery or final outcome for SAEs.

8.0 STATISTICAL METHODS

- The primary endpoint of this study is to determine the accuracy of DE CE mammography when compared to full field digital mammography (FFDM) in patients with increased breast density (BI-RADS category c or d breast density).
- The statistical analysis will focus on calculations will be performed for sensitivity, specificity, negative predictive value, positive predictive value 1 for call back (PPV1), positive predictive value 3 for biopsy performed (PPV3), cancer detection rate, false negative rate, and call back rate.

9.0 PROTOCOL AMENDMENTS AND LEGAL ASPECTS

9.1. Protocol Amendments

Neither the investigators nor the sponsor will alter this clinical study protocol without obtaining the written agreement of the other. Once the study has started, amendments should be made only in exceptional cases. The changes then become part of the clinical study protocol.

9.2 Approval of the Clinical Study Protocol and Amendments

Before the start of the study, the clinical study protocol, informed consent document, and any other appropriate documents will be submitted to the IRB with a cover letter for a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities, in accordance with local legal requirements.

The protocol cannot be activated unless documentation on all ethical and legal requirements for starting the study has been received by the sponsor. This documentation must also include a list of the members of the IRB and their occupation and qualifications. If the IRB will not disclose the names of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with Good Medical Practice. Formal approval by the IRB should preferably mention the study title, study code, study site, amendment number where applicable, and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB and, if applicable, the authorities must be informed of all subsequent protocol amendments and administrative changes, in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The investigator must keep a record of all communication with the IRB and, if applicable, between a coordinating investigator and the IRB. This also applies to any communication between the investigator (or coordinating investigator, if applicable) and the authorities.

9.3 Closure of the study

The study must be closed at the site on completion. Furthermore, the sponsor or the investigator has the right to close this study site at any time. As far as possible, premature closure should occur after mutual consultation. Depending on local legislation, it may be necessary to inform IRB and the regulatory authorities when the study site is closed.

Study materials must be returned, disposed of or retained as directed by the sponsor.

9.4 Record Retention

The investigator must obtain approval in writing from the sponsor before destruction of any records.

Essential documents should be retained until at least 5 years after the closure of the study.

Essential documents include:

- Signed informed consent documents for all patients.
- Patient identification code list and enrollment log.
- Record of all communications between the investigator and the IRB.
- Record of all communication between the investigator and the Principal Investigator or Designee.
- List of subinvestigators and other appropriately qualified person to whom the investigator has delegated significant trial-related duties, together with their roles in the study and their signatures.
- Copies of CRFs and of documentation of corrections for all patients.
- Enoxaparin accountability records.
- All other source documents (patient medical records, laboratory records, etc.).

9.5 Financial Disclosure

Before the start of the study, the investigator will disclose to the sponsor any proprietary or financial interests he or she might hold in the investigational products or the sponsor company as outlined in the financial disclosure form provided by the sponsor. The investigator agrees to update this information in case of significant changes during the study or within one year of its completion. The investigator also agrees that, where required by law or regulation, the sponsor may submit this financial information to domestic or foreign regulatory authorities in applications for marketing authorizations.

Similar information will be provided by each subinvestigator to who the investigator delegates significant study related responsibilities.

10.0 STUDY MONITORING AND AUDITING

Monitoring and auditing procedures developed or endorsed by the sponsor will be followed, in order to comply with GCP guidelines. Direct access to the on-site study documentation and medical records must be ensured.

10.1 Study Monitoring and Source Data Verification

Monitoring will be done by personal visits from a representative of the sponsor (study monitor) who will check the case report forms for completeness and clarity, and crosscheck them with source documents. In addition to the monitoring visits, frequent commutations (letter, telephone, and fax), by the study monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

Study close-out will be performed by the study monitor upon closure of the study.

10.2 On-Site Audits

Regulatory authorities, the IRB, and an auditor authorized by the sponsor may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for thee activities. Medical records and other study documents may be copied during audit or inspection provided that subject names are obliterated on the copies to ensure confidentiality.

11.0 DOCUMENTATION AND USE OF STUDY FINDINGS

11.1 Documentation of Study Findings

A case report form will be provided for each subject.

All protocol-required information collected during the study must be entered by the investigator, or designated representative, in the case report form. Details of case report form completion and correction will be explained to the investigator. If the investigator authorizes other persons to make entries in the case report form the names positions signatures and initials of these persons must be supplied to the sponsor.

The investigator or designated representative should complete the case report form pages as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

A source data location list will be prepared prior to study start. This list will be filed in both the trial master file and the investigator study file and updated as necessary.

The completed case report form must be reviewed and signed by the investigator named in the clinical study protocol or by a designated sub- **CONSENT FORM**

TITLE OF RESEARCH: Pilot study of dual-energy (DE) contrast-enhanced (CE) digital mammography to detect breast cancer in patients with increased breast density (BI-RADS category c or d).

IRB PROTOCOL NO.: F##########

INVESTIGATOR: Heidi R. Umphrey, MD, MS

SPONSOR: UAB Department of Radiology

SUPPORTED BY: AUR GE RADIOLOGY RESEARCH FELLOWSHIP AWARD

Purpose of the Research

We are asking you to take part in a research study. The purpose of this study is to find out if images from a new imaging technique called dual-energy (DE) contrast-enhanced (CE) digital mammography are comparable to routine digital mammography. This is a pilot study. A pilot study is a research study that looks at a number of patients receiving a common or routine treatment. This study will enroll 200 participants from UAB. In order to do this study, we must compare images from routine digital screening mammography to images obtained with the new technique called dual-energy (DE) contrast-enhanced (CE) digital mammography. Both techniques use small amounts of radiation to create images of your breasts.

Explanation of Procedures

If you enter the study, you have dense breast tissue and are about to have a mammogram. You may need additional views or other procedures to better evaluate any breast abnormalities that are identified. We would like to obtain an additional breast imaging study before you receive other breast imaging procedures. The additional study will require placement of an intravenous catheter or IV into a vein in your arm to administer contrast (also sometimes called x-ray "dye") within your vein similar to contrast administered during a computed tomography or CT scan. After the contrast is given through your vein, mammogram images will be taken similar to your routine screening mammogram. Both studies will be reviewed by a University of Alabama at Birmingham radiologist trained in mammography. Your primary care physician will receive your breast imaging reports and any required follow-up information as promptly as he or she usually would. Your participation in this study will consist of the additional time it takes to start an IV and obtain additional mammogram images. This can be 30 minutes to 45 minutes. Any breast abnormalities identified on either study will be further evaluated in the usual manner. Your medical record will be reviewed to determine the

results of any additional testing or biopsies. Your medical record will also be reviewed at one year to evaluate later mammography reports.

Incidental Findings

All images will be reviewed and interpreted by a University of Alabama at Birmingham radiologist trained in breast imaging.

Risks and Discomforts

There are three factors that contribute to potential risks and discomforts.

1) You will have your breast compressed for two mammography examinations. This may be uncomfortable, and you may have bruising from breast compression.
2) The extra mammogram study will expose you to additional radiation equivalent to about 6 weeks of natural background radiation. This is about the same as the amount of radiation from a conventional mammogram. Background radiation is radiation normally received from sources such as cosmic rays and natural radioactivity in building materials and the ground. There is a very small risk that the radiation may cause cancer or other radiation effects in several years.
3) You will have additional radiation equal to or slightly more than the amount you already receive for the routine screening mammography examination. Unless you have very large breasts, the additional radiation that you receive would be less than the amount of radiation that workers (such as a technologist) can receive over their whole body during a year of work. Most subjects in this study will receive additional radiation dose of 300mrads to each breast. With any radiation, current guidelines suggest that there is a very small chance of cancer induction. If you consent to participating in this study, the extra radiation you receive is small, about equal to six months of exposure to natural background radiation. For example, if two additional views of your breast are needed, then these will double the amount of radiation you receive.
4) You will have an IV placed in your arm prior to the second exam. A small amount of blood will be obtained to test your kidney function. If your kidney function is low, you may not be allowed to participate in this study. There can be pain, bruising or bleeding associated with IV placement. You will receive contrast through the IV. If you have had an allergic reaction to contrast in the past, please alert the principal investigator or research personnel as you will not qualify for this study. There is a small chance that you could have a headache, nausea, vomiting, hives, temporary low blood pressure or an allergic reaction associated with IV contrast (dye). A rare but serious risk associated with contrast administration is kidney impairment.

   The imaging procedure we are testing may involve risks that are unknown.

   Additionally, this new imaging technique being tested may identify additional lesions that require work-up. This can result in additional procedures for benign lesions.

Information for Women of Childbearing Potential and/or Men Capable of Fathering a Child

The risk to an unborn child appears very small, however, if there is a chance that you are pregnant or could become pregnant before the imaging, you may be asked to have a pregnancy test according to routine practice at UAB. If you are pregnant, you will not be allowed to participate in this study. Women who are breast-feeding and women who are pregnant are not allowed to take part in the study. If you are pregnant or become pregnant, there may be risks to the embryo or fetus that are unknown at this time.

Benefits

You may or may not benefit directly from taking part in this study. However, this study may help us better understand how to better evaluate women with dense breasts for breast cancer screening in the future.

Alternatives

Routine mammographic screening is the usual method of screening for breast cancer. The investigator or research staff will discuss this and other imaging methods with you if you have questions.

Confidentiality

Information obtained about you for this study will be kept confidential to the extent allowed by law. However, research information that identifies you may be shared with the UAB Institutional Review Board (IRB) and others who are responsible for ensuring compliance with laws and regulations related to research, including people on behalf of UAB Department of Radiology and the Office for Human Research Protections (OHRP). The information from the research may be published for scientific purposes; however, your identity will not be given out.

If any part of this study takes place at University of Alabama Hospital, this consent document will be placed in your file at that facility. The document will become part of your medical record chart.

Information relating to this study, including your name, medical record number, date of birth and social security number, may be shared with the billing offices of UAB and UAB Health System affiliated entities so that the costs for clinical services can be appropriately paid for by either the study account or by the patient/patient's insurance.

Your medical record will indicate that you are on a clinical trial and will provide the name and contact information for the principal investigator.

Monitors, auditors, the Institutional Review Board for Human Use, and regulatory authorities will be granted direct access to your original medical records for verification of trial procedures and/or data without violating confidentiality.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Information obtained during the course of the study which, in the opinion of the investigator(s), suggests that you may be at significant risk of harm to yourself or others will be reportable to a third party in the interest of protecting the rights and welfare of those at potential risk.

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with this institution. However, you should return to see the study doctor for safety reasons so you can be taken off the study drug and referred for follow-up care.

You may be removed from the study without your consent if the sponsor ends the study or if the study doctor decides it is not in the best interest of your health, or if you are not following the study rules.

If you are a UAB student or employee, taking part in this research is not a part of your UAB class work or duties. You can refuse to enroll, or withdraw after enrolling at any time before the study is over, with no effect on your class standing, grades, or job at UAB. You will not be offered or receive any special consideration if you take part in this research.

Cost of Participation

There will be no cost to you for the additional test that we are evaluating called dual-energy (DE) contrast-enhanced (CE) digital mammography

The costs of your standard medical care will be billed to you and/or your insurance company in the usual manner.

If you are in Medicare Advantage (Medicare managed care plan), you should contact someone at your plan before you start a clinical trial. They can provide more information about additional costs you could incur from participating in clinical trials.

Payment for Research-Related Injuries

UAB has not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

Significant New Findings

You will be told by your doctor or the study staff if new information becomes available that might affect your choice to stay in the study.

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, you may contact Dr. Heidi Umphrey. She will be glad to answer any of your questions. Dr. Umphrey's number is 205-996-4132. Dr. Umphrey may also be reached after hours by paging her at 205-934-3411 (beeper 8211).

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

Legal Rights

You are not waiving any of your legal rights by signing this informed consent document.

Signatures

Your signature below indicates you that you have read (or been read) the information provided above and agree to participate in this study. You will receive a copy of this signed consent form.

Signature of Participant Date

Signature of Principal Investigator Date

Signature of Witness **Date**

University of Alabama at Birmingham
AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your health information may be used for the research.

Participant Name: _____
Research Protocol: Pilot study of dual-energy (DE) contrast-enhanced (CE) digital mammography to detect breast cancer in patients with increased breast density (BI-RADS category c or d).

UAB IRB Protocol Number: F##########
Principal Investigator: Heidi R. Umphrey, MD

Sponsor: UAB Department of Radiology

What health information do the researchers want to use? All medical information and personal identifiers, including past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind related to or collected for use in the research protocol.

Why do the researchers want my health information? The researchers want to use your health information as part of the research protocol listed above and described to you in the Informed Consent document.

Who will disclose, use and/or receive my health information? The physicians, nurses and staff working on the research protocol (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, Children's of Alabama, Eye Foundation Hospital and the Jefferson County Department of Public Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees; and outside regulatory agencies, such as the Food and Drug Administration.

How will my health information be protected once it is given to others? Your health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel the Authorization? You may cancel this Authorization at any time by notifying the Principal Investigator, in writing, referencing the Research Protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the health information that was provided before you cancelled your authorization.

Can I see my health information? You have a right to request to see your health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: _____ **Date:** _____

Or a legally authorized representative: _____ **Date:** _____

Printed Name of participant's representative: _____

Relationship to the participant: _____
investigator.

The sponsor will retain the originals of all case report forms. The investigator will retain a copy of all completed case report form pages.

11.2 Use of Study Findings

All information concerning the study treatment as well as any matter concurring the operation of the sponsor, such as clinical indications of the study treatment and other scientific data relating to it, that have been provided by the sponsor and are unpublished, are confidential and must remain the sole property of the sponsor.

The sponsor has full ownership of the original case report forms completed as part of the study.

By signing the clinical study protocol, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

The sponsor will ensure that a final report on the study is prepared. The investigator (or coordinating investigator) will be required to sign a statement that he or she confirms that, to the best of his or her knowledge, it accurately describes the conduct and results of the study.

It is agreed that, consistent with scientific standards, publication of the results of the study be made only as part of a publication of the results obtained by all sites performing the protocol.

12.0 DECLARATION OF INVESTIGATOR

12.1 Declaration of Investigator

I confirm that I have read the above protocol. I understand it, and I will work according to the principles of GCP as described in 21 CFR parts 50, 54, 56, and 312 and according to applicable local requirements.

Investigator

Date:_____ Signature:_____

Name (block letters): Heidi R. Umphrey, MD

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APPENDIX A

NCI CTC (VERSION 3) TOXICITY CRITERIA

This study will utilize the CTC version 3.0 for toxicity and Adverse Event Reporting. A copy of the CTC version 3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTC version 3.0.