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A Study to Evaluate the Accuracy of a Breast Cancer Locator in Patients with Palpable Cancers

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ABBREVIATIONS

3D	three-dimensional
BCL	Breast Cancer Locator
BCS	breast conserving surgery
CCRC	Clinical Cancer Review Committee at the Norris Cotton Cancer Center
CPHS	The Committee for the Protection of Human Subjects at Dartmouth College
DCIS	ductal carcinoma in situ
DHMC	Dartmouth-Hitchcock Medical Center
DSMAC	Data Safety Monitoring and Accrual Committee
FDA	U.S. Food and Drug Administration
GCP	*Good Clinical Practice*
IRB	institutional review board
LED	light-emitting diode
MRI	magnetic resonance imaging
NCCC	Norris Cotton Cancer Center
NCI	National Cancer Institute (U.S.)
OR	operating room
SAE(e)	serious adverse event(s)
UADE(s)	unanticipated adverse device effect(s)
US	ultrasound

Section 1. INTRODUCTION

Approximately 75% of the 240,000 women diagnosed with breast cancer annually in the US choose breast conserving surgery (BCS) (1). The goal of BCS is to resect the tumor with a surrounding margin of tissue free of cancer while simultaneously preserving the overall shape and appearance of the breast. With advances in breast cancer screening techniques, many women now have malignant tumors detected before they become clinically palpable. For non-palpable lesions, localization of the tumor prior to surgery is needed. The standard technique for such patients is wire localization, in which a wire is pre-operatively placed near the tumor under mammographic, ultrasonic, or MRI guidance.

Wire localization suffers from several limitations. It adds another procedure prior to surgery, complicating and lengthening the process. It can be uncomfortable for the patient. Its biggest limitation is inaccuracy. Wire localization requires the surgeon to estimate the three dimensional (3D) position of the cancer from 2 dimensional mammography images. Wire localized excision results in positive margins approximately 30% of the time (2,3). These cases require additional surgery to remove the remaining cancer, which is both costly and emotionally difficult for patients. If 30% of the estimated 150,000 BCS cases per year in the US require re-excision, at a cost per re-excision of $11,000, the annual expense of re-excisions in the US is approximately $500,000,000.

Alternatives to wire localization have been tested. Intraoperative ultrasound has been shown to be superior to wire localization (4-5). Unfortunately, most ductal carcinoma in situ (DCIS) and some invasive cancers that are mammographically visible are not evident on ultrasound.

Magnetic resonance imaging of the breast has been shown to be more sensitive than ultrasound or mammography for the detection of cancer (6). Breast cancer size, as determined by histopathology, is also more accurately defined by MRI than by mammography or US (7-9). Several groups have shown that the superior tumor visualization resulting from preoperative prone MRI results in changes in the operative plan in 20-25% of cases (10-12). Despite this evidence, the use of MRI has not been demonstrated to produce better short-term outcomes: the prospective randomized COMICE trial failed to demonstrate a decrease in the positive

margin rate and need for re-excision with the use of pre-operative prone MRI (13). The COMICE study authors recognized that the inability of prone MRI to result in decreased positive margin rates might be due to the way the imaging data is presented to the surgeon, stating that “techniques to ensure surgical precision is at an optimum need further examination” (13). The shape of the breast during prone MR imaging (with the breast pendant in a bilateral imaging coil) is radically different from the supine, arm-extended position in the operating room.

Supine MRI more accurately replicates the surgical position. Indeed, a study by Sakakibara, *et al.* (14) randomized patients with small foci of DCIS to undergo wire localized or supine MRI guided BCS and found the positive margin rate and resected tissue volume were lower in patients undergoing supine MRI guided excision. A more recent non-randomized study of patients with larger foci of DCIS by these same investigators has also been reported (15).

We recently developed a method of MRI-guided BCS that incorporates preoperative supine MRI to define tumor extent and uses an intraoperative optical scan to adjust the MRI image to the exact breast position in the OR (16). This localization technique provides the surgeon with three dimensional views and measurements of tumor shape and position within the breast as it appears during surgery. When combined with intraoperative tracking technology, we showed in a pilot study of 18 patients that this approach enabled us to localize breast cancer as accurately as by palpation (16). We are currently funded by the NCI via an R21 grant and are actively accruing patients to a randomized clinical trial (D0928) which compares supine MRI/optical scanning/intra-operative tracking localization to wire localization for patients with non-palpable breast cancer.

Although our supine MRI/ optical scanning/ intra-operative tracker technology is accurate, it has some limitations that may limit its widespread utilization. The software that modifies the MRI image into the intra-operative acquired scanned image is complicated and currently requires the surgeon have intra-operative technical assistance. The current system only generates an outline of the tumor on the breast surface, but does not provide any guidance for the surgeon when operating inside the breast.

We have now invented a device, the Breast Cancer Locator (BCL) which overcomes these limitations. BCL uses 3D printing to create a bra-like plastic form that matches the breast

surface when the patient is in the supine MRI (and surgical) position. This locator can be constructed pre-operatively, sterilized and provided to the surgeon at the time of procedure. The outline of the breast cancer on the breast surface at the point where the cancer is closest to the skin is built into the locator, so that the surgeon can simply apply the locator to the patient's breast and trace the tumor outline on the skin. The locator also contains 5 cylinders which project outward from its surface. A needle will be placed in each cylinder. The depth and angle that the needle passes into the breast is controlled by the angle and length of the cylinder. The surgeon will inject a small amount of blue dye at each site, creating a 1 cm diameter blue spot in the breast parenchyma. The spots will be made 1 cm away from the medial, lateral, cranial, and caudal tumor edges as defined by the supine MRI. A fifth cylinder will allow the surgeon to place a needle and make an injection of blue dye 1 cm superficial to the tumor. After the blue dye is injected, a hook wire will be deployed through this needle into the MRI defined center of the tumor. When the BCL is removed, the hook wire will remain, indicating the direction from the skin surface, through the blue spot superficial to the tumor, to the center of the tumor. With these landmarks established, the surgeon will then be free to move the patient on the OR table (e.g., place the arm out to the side, rotate the patient to one side or the other) to facilitate surgery.

When the breast is marked by the BCL, the surgeon will then have the standard wire localizing the cancer which they are used to. This wire will be placed at least as accurately as it is currently being placed by Radiologists (who are relying on spot mammographic, US or MRI images to try to localize the cancer or the clip left behind at the time of initial biopsy (which might not have deployed at the center of the cancer)). When placed by the BCL the wire will give surgeons directional information from the skin at the incision site towards the center of the cancer. When wires are placed pre-operatively by Radiologists the wire is commonly placed by Radiologists such that it enters the skin far away from the site of the incision. The surgeon will now also have additional information to guide the cancer excision. The projected edges of the often irregularly shaped breast tumor will appear on the surface of the breast. The surgeon will also now have landmarks inside the breast to ensure that the desired amount of tissue around the tumor is removed.

We propose to test the accuracy of the BCL in patients who have palpable tumors, so that the guidance provided by the BCL is not necessary for the surgeon to resect the cancer

accurately. If the BCL places the ink spots with perfect accuracy and the surgeon perfectly accurately follows the spots to do the excision, the margins may still be positive when the tumor histologically extends past its edges as defined by MRI. To estimate how often this may happen, we reviewed data on 27 patients from our pilot study of the supine MRI/optical scan/tracker system on patients with palpable cancers (16) and data from our current study of this system on patients with non-palpable cancers. The MRI diameter was larger than the pathologic diameter in 13 cases; the median overestimate in diameter was 4 mm. The MRI diameter was smaller than the pathologic diameter in 14 cases; the median underestimate was 5 mm. The pathologic tumor diameter was more than 2 cm greater than the MRI diameter in only 1 case (4%). Upon review of the literature, Boetes *et al.* evaluated 60 breast cancers; in only 1 patient was the pathologic tumor diameter greater than 2 cm larger than the diameter on MRI (8). In another study, 2 of 68 pts had pathologic diameters more than 2 cm greater than the diameter on MRI (7). Thus, if one were to excise 1 cm on each side of the MRI defined tumor, one would expect the histologic margin to be positive because of the inability of MRI to detect tumor in roughly 5% of patients.

In this study, we will enroll women with *palpable* cancers to assess the accuracy of the BCL and concomitant procedure as a vehicle to optimize and validate the approach in surgical cases where the new device will not substantially alter or modify the standard-of-care procedure before initiating an evaluative trial of the BCL in *non-palpable* breast cancer cases. Taking this path towards clinical evaluation also does not interrupt or otherwise compete for patients with our ongoing R21-funded clinical study D0928, which enrolls patient with *non-palpable* cancers.

Section 2. OBJECTIVES

We propose to test whether the Breast Cancer Locator (BCL) accurately defines the edges of the cancer. Twenty patients with palpable invasive breast cancer will undergo pre-operative supine MRI, creation of a BCL, and breast surgery using the BCL as an adjunct to palpation-guided tumor resection. Patients will also have the tumor position on their skin localized with the supine MR/optical scan/tracker method.

The primary objective is to measure the distance from the center of the spots made by the BCL to the cancer edges.

Our secondary objectives are to determine:

1. the pathologic final margin (distance from the tumor to the specimen edge).
2. the difference between the medial, lateral, cranial and caudal tumor edges as defined by the BCL and the supine MR/optical scan/tracker system.
3. lumpectomy specimen volumes.

Section 3. ELIGIBILITY CRITERIA

1. Age $\geq$ 18 years
2. Histologic diagnosis of palpable invasive breast cancer or ductal carcinoma in situ
3. Patient desire to undergo breast surgery
4. Ability to voluntarily provide informed consent to participate prior to any study-related assessments/procedures being conducted
5. The cancer enhances on breast MRI imaging.

Exclusion Criteria

1. Absolute contraindication to MRI, including presence of implanted electrical device (pacemaker or neurostimulator), aneurysm clip, or metallic foreign body in or near eyes
2. Severe claustrophobia
3. Contraindication to use of gadolinium-based intravenous contrast, including life-threatening allergy or compromised renal function (creatinine > 2.0)
4. History of median sternotomy
5. Pregnancy. Patient attestation that they are not pregnant will be acceptable as per standard policy for MRIs at DHMC.

An eligibility worksheet will be completed for each patient prior to enrollment and will be signed and dated by the surgeon investigator.

Section 4. TREATMENT PLAN

Patients with a percutaneous core biopsy demonstrating invasive carcinoma or ductal carcinoma in situ will undergo contrast-enhanced bilateral breast MRI in the prone position, which is the current clinical standard at Dartmouth. At the time of surgical consultation, patients with palpable invasive breast cancer or DCIS who desire breast surgery will be invited to be a part of the study. Prior to surgery, these patients will undergo a contrast-enhanced supine MRI and an optical scan of the breast while in the same position during the MRI using the GO!Scan 3D optical scanner (Creaform, Levis, Québec, Canada). The study Radiologist will outline the tumor edges on the supine MRI. These supine MRI images will be used to create a Breast Cancer Locator (BCL) using 3D printing. The printed product will include a surface which will fit over the breast, with a cut-out for the nipple and a 5 mm opening located 4 cm directly vertical from the nipple (which will allow the surgeon to be sure the locator is positioned accurately on the breast). The BCL will also contain a cut-out for the surgeon to draw the tumor image on the breast surface, and 5 cylinders to guide needle injections of dye to define the cancer edges. It will also contain the printed surface of the tumor, which will be connected to the surface of the tumor locator by a removable cylinder, and will enable the surgeon to have a visual model of the cancer in the breast. The BCL will be sterilized using standard microwave techniques for use in the Operating Room (OR).

In the OR, the patient will undergo general anesthesia. The patient's arm will be placed out to the side in the surgical position. The GO!Scan 3D optical scanner will be used to scan an image of the breast. The tumor location defined by the supine MRI images will be transposed into the optically scanned image with software we are using in our current trial (D0928) and displayed for the surgeon. Using a tracker, the surgeon will mark the medial, lateral, cranial and caudal edges of the tumor on the breast skin.

The patient will then be prepped and draped. The patient's arm, attached to an arm board, will be moved parallel to the OR table, so that it is in the approximate position as when the supine MRI was performed. The BCL will be positioned on the breast, using the nipple and

a point drawn 4 cm directly vertical from the nipple to ensure accurate positioning, and will be secured in place. The outline of the cancer on the breast surface will be drawn by the surgeon. Four injections of 0.02 ml of methylene blue dye (Methylene Blue Injection, 1% Akorn, Inc Lake Forest, IL) will be made by the surgeon using a 21 gauge needle of appropriate length to create spots to delineate the cranial, caudal, medial and lateral tumor margins. An additional methylene blue dye injection will be made to delineate the superficial margin. The fifth needle port will then be partly detached so that a second needle can be placed through this port into the MRI defined center of the cancer and a hook wire will be placed inside this needle and deployed in the center of the tumor. The BCL will then be removed and the distances from the medial, lateral, cranial and caudal edges as determined by the BCL will be compared to the edge locations determined by the optical scan/tracker method.

The surgeon will then perform either a breast conserving tumor resection or a mastectomy. The objective of the breast conserving resection will be to remove approximately 1 cm of normal feeling breast tissue around all of the palpable tumor edges as per standard-of-care. For breast conserving resections, the specimen volume will be determined by water displacement and specimen scanning using the GO!Scan. The location of the 4 horizontal blue dye spots in the specimen will be identified by the surgeon with black silk sutures; the location of the superficial blue dye spot will be marked with a white VICRYL suture. The specimen surfaces will be inked with 6 different colors, as per standard Dartmouth protocol. Specimen mammograms will be obtained and then the specimen will be sent to Pathology.

Mastectomy specimens will be sent to Pathology and inked with blue ink on the superficial surface and black ink on the deep surface. The surgeon will then perform a breast conserving resection on the mastectomy specimen in Pathology. The goal of this procedure will be to remove approximately 1 cm of normal tissue around the tumor and to identify the blue dye spots and place marking sutures in the same way that they will be placed on breast conserving resection specimens. The specimen volume will be determined, margins will be inked with 6 colors and a specimen mammogram will be obtained.

In Pathology, the specimen will be cut along the horizontal plane defined by the black silk sutures. The pathologist will place black-inked pins through the middle of the blue dye spots. A photo will be taken of the tissue slice showing the tumor in the middle with the 4 blue

dye spots with pins in place. When tissue sections are cut, the black ink from the pins will appear on the sections, allowing the pathologist to measure the distance from the pin to the tumor. An additional cut will be made to include the white vicryl suture, in a plane perpendicular to the one defined by the black silk sutures. A black inked pin will be placed through the middle of this superficial blue spot, a photo will be taken of the tumor and this pin, and a section will be cut so the pathologist can measure the distance from this pin to the tumor.

Margins for invasive cancers will be considered positive if cancer cells are present at any of the edges of the specimen slices. Margins will be considered positive for DCIS if there are tumor cells < 1 mm from the edge. The distance to the nearest margin will be determined in all cases.

Section 5. POTENTIAL TOXICITY

Supine MRIs are administered according to standard-of-care practice for prone breast MRI and represent no more additional risk than would be experienced by women receiving these exams as part of their (non-research) breast care. The risk of contrast enhanced MRI is very low, reflecting the minute risk of life-threatening allergy and development of nephrogenic sclerosis related to gadolinium-based intravenous contrast. Patients deemed to be at higher risk for gadolinium-induced nephrogenic sclerosis because of compromised renal function will not be eligible for participation. Patients who experience a significant allergic reaction to gadolinium-based intravenous contrast at the time of their clinical prone MRI will also be considered ineligible for study participation.

Optical scans will be performed using a GO!Scan 3D optical scanner (Creaform, Levis, Québec, Canada). This scanner is able to scan the entire breast in 1 minute. It uses white light (LED) to form the image, like a flashlight. No anticipated risks are associated with the use of this scanner.

Participants will be undergoing surgical excision of their breast cancer regardless of their participation in this study. The risks of surgery include a low chance of bleeding or infection. We are performing this study on patients with palpable cancers because the surgeon does not need imaging information to excise palpable cancers: the extent of surgery is guided

by the edges of the tumor mass palpated at the time of surgery. Therefore, even if the Breast Cancer Locator is inaccurate, no negative consequences will be experienced by the patient.

Methylene blue dye is approved for use in humans and has minimal toxicity (17-21). It has been used for many years for routine identification of sentinel nodes in breast cancer patients. Transient blue staining of the skin may be seen with injections close to the skin. Potential serious adverse effects are very rare and include one case of skin necrosis with intradermal injection and 2 case reports of possible anaphylactic reactions.

5.1 Reporting Requirements for Unanticipated Adverse Device Effects (UADEs)

Adverse events and unanticipated problems will be reported to The Dartmouth Committee for the Protection of Human Subjects (CPHS) as per their statement found at http://www.dartmouth.edu/~cphs/docs/aedsmmemo.pdf using their *CPHS – UPIRSO, SAE, UADE Reporting Form* found at http://www.dartmouth.edu/~cphs/tosubmit/forms/. UADEs should be reported as soon as possible, but no later than 10 working days after the investigator learns of the effect.

Adverse effects to be reported to the CPHS are: any adverse experience, defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research), that is considered:

- Serious: Death; a life-threatening adverse drug experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability or incapacity; or a congenital anomaly or birth defect; and
- Unexpected: Any adverse experience, the specificity or severity of which is not consistent with the current investigator brochure or consent form; and
- Possibly related: There is a reasonable possibility that the incident, experience, or outcome may have been associated with the procedures involved in the research; and
- is experienced by a participant in a trial open at a site subject to review by the CPHS.

The following definitions will be used to assess causality:

- No: The clinical adverse event is definitely unrelated to study procedures (e.g., does not follow a reasonable temporal sequence from study procedure, present prior to procedure, etc.)
- Unlikely: The study procedures do not have any reasonable association with the observed experience; however, relationship cannot be definitely excluded.
- Possibly: The connection with study procedures appears feasible, but cannot be excluded with certainty (e.g., follows a reasonable temporal sequence from procedure, but may also be related to other known factors).
- Probably: The clinical experience appears related to the study procedures with a high degree of certainty (e.g., follows a reasonable temporal sequence from procedure and abates upon termination of the procedure, cannot be reasonably explained by known characteristics of the patient's clinical state or other modes of therapy administered to the patient, etc.)

An unanticipated problem involving risks to subjects or others is defined as any incident, experience, or outcome that meets each of the following criteria:

- Unanticipated in terms of nature, severity, or frequency given: (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and consent document; and (b) the characteristics of the subject population being studied; and
- Possibly related to participation in the research means there is a reasonable possibility that the incident, experience, or outcome may have been associated with research participation; and
- The problem suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, emotional, economic, legal, or social harms) than was previously known or recognized.

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Section 6. DEVICE FORMULATION AND PREPARATION

Supine MRI images will be obtained on a Phillips 3T MRI scanner using two circular Philips SENSE Flex-M coils (2-element phased array receive-only coils) prior to and following an intravenous gadolinium–based contrast agent. Prior to scanning, 8 fiducial markers will be placed on the skin in standardized locations. A pre-injection T1 weighted ultrafast gradient echo sequence will be used to define the breast volume and tissue structures. A post-injection T1-weighted turbo gradient-echo volume acquisition with fat saturation will be used to determine tumor location and shape.

Supine MRI images will be used to create a Breast Cancer Locator using 3-dimensional printing. The printed product will include a surface that will fit on the breast, a cut-out for the nipple and for a spot 4 cm directly vertical from the nipple (to ensure that the BCL is positioned accurately on the breast surface), a cut-out for the surgeon to draw the tumor image on the breast surface, and 5 cylinders to guide needle injections of dye to define the cancer edges. A needle will be placed in each cylinder. The depth and angle that the needle passes into the breast is controlled by the angle and length of the cylinder. Needles will be 21 gauge in diameter and of sufficient length. A syringe will be included which will allow accurate injection of 0.02 ml of methylene blue dye. The surgeon will inject the blue dye at each site, creating a 1 cm diameter blue spot in the breast parenchyma. The spots will be made 1 cm away from the medial, lateral, cranial and caudal tumor edges as defined by the supine MRI. All of these spots will be in the same cross-sectional plane. This plane will be perpendicular to a line formed from the center of the tumor to surface of the skin at the location where the tumor is closest to the skin. The fifth cylinder will allow the surgeon to inject methylene blue dye 1 cm superficial to the tumor and will allow a second needle to be placed from the skin into the MRI defined center of the tumor.

The BCL will also contain the printed surface of the tumor, colored differently, which will be connected to the surface of the tumor locator by a removable cylinder. This form will enable the surgeon to have a visual model of the cancer in the breast.

Each BCL will undergo quality assurance testing prior to use. Defined length and bore needles will be placed into each of the cylinders and the distance from the tip of the needle to the tumor will be measured. A BCL will only be used if this distance is within 2 mm of the

expected distance as calculated by the MRI model. In the case of irregularly shaped tumors this distance may be greater than 1 cm. The tumor locator will be sterilized using standard microwave techniques for use in the OR.

Sections 7 and 8. Clinical ENDPOINTS AND STATISTICAL ANALYSIS

Our primary objective is to determine the accuracy of the Breast Cancer Locator (BCL). The primary outcome measure is the distance measured by Pathology from the tumor edge to the center of the ink spots, as marked by the black inked pins. Five (5) measurements will be made per patient. The BCL will be considered accurate if all 5 measurements are > 0 cm from the tumor edge.

As discussed in the Introduction, we expect that in approximately 5% of patients the pathologically determined tumor diameter will be at least 2 cm greater than the MRI defined diameter; thus even if a 1 cm margin around the MRI defined tumor edge was excised, a positive margin (a distance of zero or less) would be expected in 5% of patients. We will evaluate the accuracy of the BCL after the first 10 patients. If the BCL is accurate in < 80% of patients, we will make modifications in the locator and test an additional 10 patients. If it remains inaccurate, additional modifications may be made and additional patients may be accrued to this study up to a maximum of 50 patients. If the measurements are accurate in 80% of patients or more of the patients in a test cohort of ten patients, we will accrue an additional 10 patients to confirm the finding. Once the accuracy is determined to be $\geq$ 80% in 20 patients we will terminate accrual.

The modifications we make in the BCL will be based on a thorough review of each case that was inaccurate. We will review every step in the process, including the definition of the cancer edges by Radiology, the quality assurance testing of the manufactured BCL (Section 6, P. 13), the pin placement in the ink spots and edge measurement by Pathology, and whether the cases represent unusual cancers where the pathologic extent of the tumors exceeds the extent visible on MRI (e.g., Infiltrating lobular cancer). We may discover an unforeseen design flaw in the methodology or product manufacture that will only become evident once we start to use it.

Annually at Dartmouth we care for approximately 300 patients with invasive ductal cancer and 100 patients with DCIS. Approximately 2/3 of these patients (266) will undergo breast conserving surgery. Approximately 1/4 of these patients will have palpable tumors (67). We anticipate that it will be possible to accrue one half (33) of these patients per year. Thus, we expect that it will take 8 months to complete accrual of 20 patients.

We plan to use the accuracy information from this trial to support a larger multi-institutional or randomized study of the use of the Breast Cancer Locator in patients with non-palpable breast cancer. We anticipate that the main outcome measure of the next, larger trial, like our current trial of the supine imaging/optical scan and intra-operative tracker system (D0928, phase II), will be the positive margin rate.

Secondary endpoints will be analyzed as follows. One secondary outcome measure will be the positive margin rate as defined by standard pathologic evaluation of the entire specimen. Our senior breast Pathologist, Dr. Wendy Wells, has performed a detailed analysis of the surgical margins for patients who had a core biopsy which was positive for cancer or DCIS and then underwent partial mastectomy at Dartmouth in the year 2005. A total of 125 patients with invasive ductal carcinoma were identified: 31 (25%) had positive margins. Twenty six of 53 patients undergoing partial mastectomy for DCIS had positive margins (45%). Overall, 57/178 patients (32%) had positive margins. A two-thirds decrease in the positive margin rate (i.e., from 32% to 11% or less) would be clinically meaningful.

Another secondary outcome measure, the distances between the specimen edges as determined by the Breast Cancer Locator and by the supine MRI/optical scan/ tracker system, will be measured and descriptive statistics will be employed. We will conclude that the two methods of depicting the tumor edges on the breast skin surface are equivalent if the mean distances between the edges are < 5 mm.

We also wish to minimize the excision of normal breast tissue around the cancer. Lumpectomy specimen volumes will be measured and descriptive statistics employed. Measured specimen volumes will be compared to theoretical ideal specimen volumes generated by calculating the volume of the tumor specimen with 1 cm added to all of its surfaces based on the supine MRI.

Relevant data will be saved in Velos electronic case report forms.

Section 9. SAFETY AND DATA MONITORING

This study will be monitored by the Data Safety Monitoring and Accrual Committee (DSMAC) of the Norris Cotton Cancer Center. The Committee meets quarterly to review accrual rates and information for studies that have accrued participants. The Clinical Cancer Review Committee (CCRC) determines the frequency of DSMAC review. The DSMAC has the authority to suspend or to recommend termination to the CCRC of all research activities that fall within its jurisdiction. In the event that a study is suspended or terminated, that information will be forwarded to the CPHS (Dartmouth IRB) office.

Section 10. ON-SITE MONITORING

Clinical research monitoring for regulatory compliance and data integrity will be conducted according to the NCI-approved NCCC *Data and Safety Monitoring Plan*. Internal monitoring is conducted by appropriately trained staff of the NCCC Office of Clinical Research and Dartmouth-Hitchcock Medical Center Clinical Trials Office (CTO(who are not involved in the study. This monitoring will include periodic assessment of the regulatory compliance, data quality, and study integrity. Study records will be reviewed and directly compared to source documents and the conduct of the study will be discussed with the investigator. Monitors may request access to all regulatory documents, source documents, CRFs, and other study documentation for on-site inspection. Direct access to these documents is guaranteed by the investigator, who must provide support at all times for these activities.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Dartmouth research compliance and quality assurance offices. The investigator will permit study protocol related audits and inspections by the Dartmouth CPHS, government regulatory bodies, and the Dartmouth compliance and quality assurance groups of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., diagnostic laboratory).

Section 11. RECORD RETENTION

Following closure of the study, the investigator will maintain all site study records In a safe and secure location. The records are maintained to allow easy and timely retrieval when needed (e.g., audit or inspection) and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Upon completion of study analysis, research information is stored in Dartmouth College Records Management off-site storage located at 6218 Etna Road, Hanover, NH. Documents are shredded on site after 50 years of storage.

Electronic case report forms, participant, and study information will be kept in the Velos eResearch password-protected database (or equivalent) indefinitely.

Section 12. HUMAN SUBJECTS

The patients for this study will be accrued from the population treated at the Dartmouth-Hitchcock Medical Center. All patients will sign an informed consent, which describes the treatment to be performed and discusses the risks and benefits of participation in the study.

Patients must give a statement of informed consent. The informed consent must meet the requirements of the FDA (21 CFR 50.25 Elements of Informed Consent) and the Committee for the Protection of Human Subjects at Dartmouth College, the Dartmouth-Hitchcock Medical Center IRB. Before initiating a trial, the investigator will have written and dated approval from the CPHS for the trial protocol, amendment(s), written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and written information to be provided to subjects. The investigators, or a person designated by the investigators, will explain the benefits and risks of participation in the study to each subject (and impartial witness when applicable) and obtain written informed consent prior to the subject entering the study (i.e., before initiation of non-routine tests and administration of study drug). The final form must be agreed to by the CPHS and must contain all elements in the sample form, in language readily understood by the subject. Each subject's original consent form, signed and dated by the subject and by the person who conducted the informed consent

discussion, will be retained by the investigator. In addition, a copy of the informed consent will be given to the subject.

Risk/Benefit analysis:

Risks associated with this study include the risks of an additional MRI and all participants have potential confidentiality risks. Even if the Breast Cancer Locator is highly inaccurate, this will pose no additional risk to the patient because the surgeon is going to plan their resection by taking a suitable margin (approximately 1 cm) of normal feeling breast tissue all around the palpable edges of the tumor. Methylene blue dye is approved for use in humans and has been used for many years to identify sentinel nodes in breast cancer patients. Methylene blue is considered to be the safest blue dye to use for sentinel node identification and has minimal toxicity. Patients may experience a transient blue discoloration of the skin. Potential serious adverse effects are very rare: one case of skin necrosis with intradermal injection has been observed and two cases of possible anaphylaxis have been reported (18-21). The risk of an additional MRI is negligible and reflects the minute risk of life-threatening allergy and development of nephrogenic sclerosis related to gadolinium-based intravenous contrast. Patients deemed to be at higher risk for gadolinium-induced nephrogenic sclerosis because of compromised renal function will not be eligible for participation. Patients who experience a significant allergic reaction to gadolinium-based intravenous contrast at the time of their clinical prone MRI will also be considered ineligible for study participation.

Risk of breach of confidentiality of the medical records of participants will be minimized. Subject identity is numerically coded and is not available to research investigators or otherwise stored on the databases maintained by the researchers to archive the clinical encounters accrued as part of the studies conducted under this protocol. In this regard, all conventional clinical image data is de-identified prior to its use for analysis. Databases which are used to store subject-sensitive information, even though completely de-identified as stored, are password-protected and encrypted during file/data transfers from viewing terminals. As further safe-guard, the Data Safety Monitoring and Accrual Committee of the Norris Cotton Cancer Center will oversee the conduct of the trial.

The importance of the knowledge to be gained and the ultimate potential for benefit for future patients if this new technology is effective far outweighs the nominal risks experienced

by the women who participate in this clinical study.

Pregnant women will be excluded due to the potential risk of gadolinium to the fetus.

Women with child-bearing potential are eligible for enrollment into the study. The risks of participating in the imaging sessions for these women are no greater than for any other participant. Risks associated with breast surgery vis-à-vis child-bearing potential are outlined as part of standard of care. Thus, any woman of child-bearing years enrolled in this protocol would already understand (and have accepted) the surgical risks to her fertility.

Only women will be enrolled in the study because breast cancer is predominantly a female disease. The imaging apparatus is design to accommodate the size and shape variations associated with the adult female breast. While a very small proportion of breast cancer appears in males, the imaging systems are not designed to image the male breast. All racial and ethnic categories will be recruited commensurate with the racial/ethnic composition of the DHMC patient catchment area.

Patients will be considered “on study” and will be monitored for adverse events by the operating surgeon from the time of registration until 2 weeks after surgery.

Section 13. OBLIGATIONS OF INVESTIGATORS

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the *Code of Federal Regulations* and/or the *Declaration of Helsinki.* The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all

case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

Section 14. REFERENCES

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