ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A221702

ARM: AXILLARY REVERSE MAPPING – A PROSPECTIVE TRIAL TO STUDY RATES OF LYMPHEDEMA AND REGIONAL RECURRENCE AFTER SENTINEL LYMPH NODE BIOPSY AND SENTINEL LYMPH NODE BIOPSY FOLLOWED BY AXILLARY LYMPH NODE DISSECTION WITH AND WITHOUT AXILLARY REVERSE MAPPING

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Study Resources:

Expedited Adverse Event Reporting

[redacted]

Medidata Rave® iMedidata portal

[redacted]

OPEN (Oncology Patient Enrollment Network)

[redacted]

Biospecimen Management System

[redacted]

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Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox [redacted]
Questions regarding drug administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at [redacted] and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at [redacted] Contact the CTSU Help Desk with any OPEN related questions by phone or email : [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions. Do not submit study data or forms to the CTSU. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website [redacted] Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e., patient eligibility or treatment-related) see the Protocol Contacts, Page 2.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or email: CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.		

ARM: AXILLARY REVERSE MAPPING – A PROSPECTIVE TRIAL TO STUDY RATES OF LYMPHEDEMA AND REGIONAL RECURRENCE AFTER SENTINEL LYMPH NODE BIOPSY AND SENTINEL LYMPH NODE BIOPSY FOLLOWED BY AXILLARY LYMPH NODE DISSECTION WITH AND WITHOUT AXILLARY REVERSE MAPPING

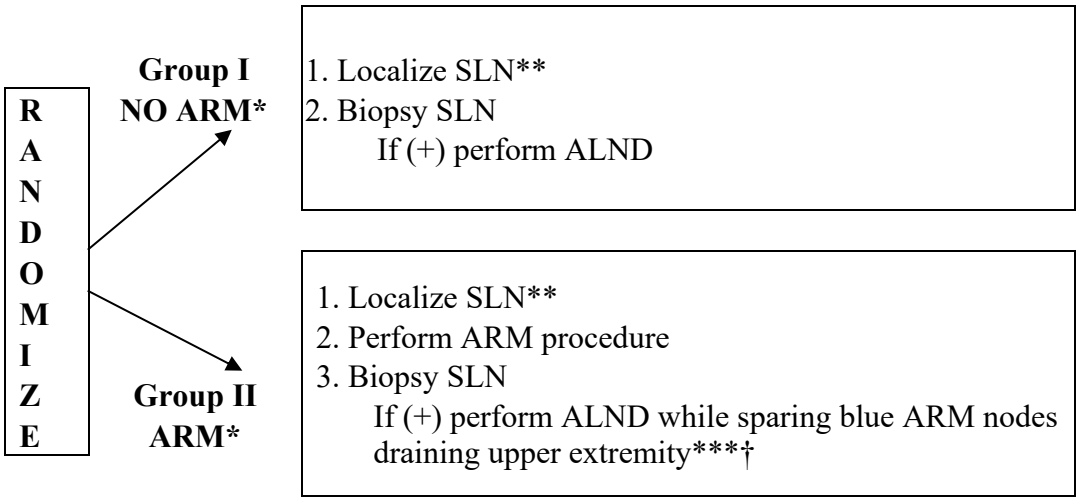
Eligibility Criteria (see Section 3.0)

- Documentation of Disease: cT1-3 patients undergoing axillary surgery. (See §3.2.1)
- Prior Treatment: No prior axillary surgery except needle biopsy or concurrent SLNB (See §3.2.2)
- No prior history of ipsilateral breast cancer (invasive or DCIS). LCIS and benign disease are allowed. (May have neoadjuvant chemotherapy) (See §3.2.3)
- No bilateral invasive breast cancer (See §3.2.4)
- No matted nodes (See §3.2.5)
- No history of lymphedema of either arm (See §3.2.6)
- No known allergies to make-up or blue dyes or allergies to dyes used in tattoos (See §3.2.7)
- Patients must be able to speak and/or read English (See §3.2.8)
- Female (See §3.2.9)
- Age ≥18 years. (See §3.2.10)
- ECOG Performance Status 0, 1 or 2 (See §3.2.11)

Required Initial Laboratory Values
Creatinine ≤ 1.5 x upper limit of normal (ULN)

Schema

Schema I for Patients Undergoing Mastectomy



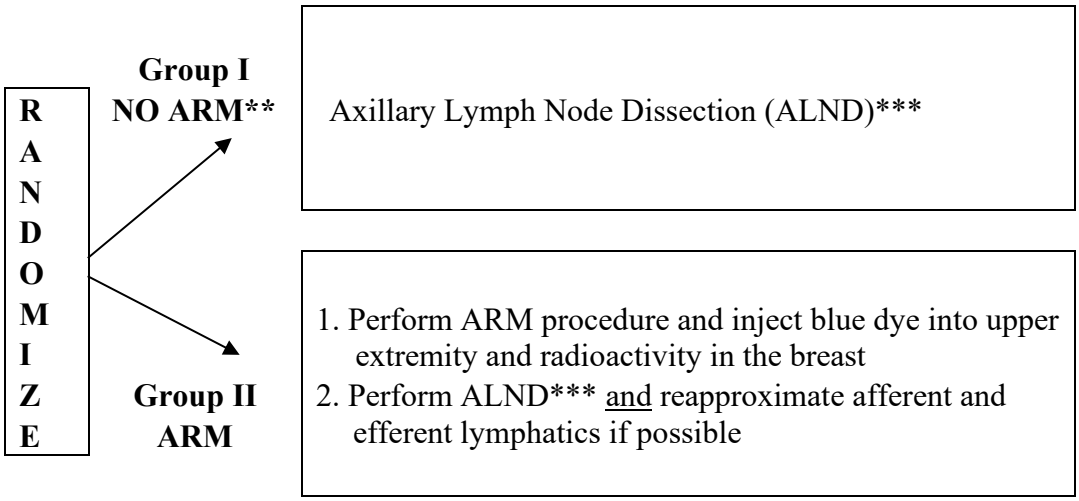
* ARM: Axillary Reverse Mapping

** If sentinel lymph node (SLN) cannot be localized by radioactive isotope alone, and blue dye is injected into the breast to identify the SLN, ARM procedure cannot be performed

*** If SLN nodes are ARM nodes, remove and determine pathology. If positive, perform axillary lymph node dissection (ALND) and reapproximate afferent and efferent lymphatics of the ARM nodes.

† If ALND is performed during a separate operation, ARM procedure must be repeated.

Schema II for Patients Undergoing Breast Conserving Surgery *



* Patients planning for ALND (See Section 3.2.1)
** ARM: Axillary Reverse Mapping
*** May be performed with or without a sentinel lymph node biopsy (SLNB)

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Surgical credentialing must be completed before any patients can be registered to the trial. Please see Section 14.0 for credentialing requirements.

It is expected that surgery be performed at the registering institution. Radiation therapy may be administered at external radiation therapy facilities, if they meet the requirements outlined in Section 7.5. Chemotherapy may be administered at a non –registering institution.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

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1.0 BACKGROUND

1.1. Rationale for proposed study

Lymph node status is a key prognostic variable, and therapeutic decisions are based on the presence or absence of breast cancer cells metastatic to the axillary lymph node(s). The results of randomized prospective clinical trials, which guide current therapy, have been based on the pathologic status of the axillary lymph nodes. Although newer markers of oncogene expression show promise with respect to the treatment of breast cancer, the status of the axillary nodes remains an important prognostic criterion and will continue to have a direct impact on clinical decisions.

When necessary, the prescribed technique for axillary lymph node dissection (ALND) has changed little over the last several decades. The principal features include removal of axillary tissue inferior to the axillary vein, medially to the medial border of the teres minor muscle, lateral to the serratus muscle, and anterior to the teres major muscle. (1) The standard teaching was that the lymphatic ran along the inferior side of the axillary vein (Figure 1) and avoiding skeletonizing the vein would prevent lymphedema. The morbidity and risks of an ALND include the risk of general anesthesia, permanent hypesthesia and/or dysesthesia at the posterior aspect of the upper extremity (UE) (2), painful neuroma, post-operative seroma formation (3), and lymphedema of the UE (4)—the risk of which increases with greater extent of axillary node resection as well as breast surgery. (5,6) It has been reported that 82% of women experience at least one problem with their UE following ALND. Patients often have decreased mobilization of the shoulder and require physical therapy to regain full function of the upper extremity. Associated psychological distress ranges from 17% to 50%. (7, 8) Depending on how it is defined, lymphedema alone has been reported to be as high as 77% (Table I). (9-18) Routine use of sentinel lymph node biopsy (SLNB) has drastically reduced this risk but is still quite variable (0-13%). The wide variability with both SLNB and ALND indicate a concomitant wide variability in technique in performance of these procedures. Therefore, a modification of surgical technique that can reproducibly reduce lymphedema (LE) is necessary.

The proposed research attempts to establish the safety and efficacy of a new procedure, axillary reverse mapping (ARM), to prevent one of the major surgical side-effects of lymphadenectomy (SLNB or ALND)—lymphedema of the Upper Extremity (UE).

Present day SLNB or ALND doesn't take into account the anatomical drainage from the breast versus that of the UE because drainage from the UE into the axilla has only recently been published. (19-24) Yet, surgical lymphedema likely results from transection of lymph vessels from the UE coursing through the axilla and is perhaps the most prominent complication resulting from SLNB or ALND. (22) From its inception, SLNB, developed to prevent the high morbidity seen with ALND (Table I) has been assumed to be less morbid, but still itself results in a high rate of lymphedema. Because of the long-term sequelae of lymphedema, this surgical outcome is an important measurement when a replacement procedure for SLNB or ALND is evaluated. Several cooperative group trials have shown lymphedema rates in approximately the five to seven percent range at 6 months to a year with SLN biopsy alone. (16, 18, 25) In the American College of Surgeons Oncology Group Z0010 prospective observational study (25), 2904 patients had UE circumference data recorded, both before surgery and six months after SLNB. Lymphedema was defined in this study as a change in UE circumference of >2 cm when compared with the contralateral or control UE and with baseline measurements. Nearly seven percent of the patients had a change in UE circumference >2 cm. Multiple comparison studies, several of which were randomized, have confirmed that SLNB consistently has lower morbidity and lymphedema rates than ALND (Table I). Lymphedema in ALND groups ranges from 13 to 77%, varying with how closely lymphedema was monitored, length of follow-up (4,26),

questionably the number of positive lymph nodes (27), post-operative irradiation (5,28), extent of surgery and body habitus and a number of other patient characteristics. (26, 29) Although the lymphedema rate was much lower with the SLNB, it was still clinically significant with a range of 0 to 13%. Table I demonstrates lymphedema rates in several large randomized trials.

Lymphedema Studies

Study	SLNB (#)	ALND (#)	Lymphedema SLNB (%)	Lymphedema ALND (%)
Schrenk 2000	35	35	0	17
Haid 2002	57	140	4	27
Swenson 2002	169	78	4	14
Blanchard 2003	683	91	6	34
Schijven 2003	180	213	1	7
Ronka 2005	43	40	13	77
Leidenius 2005	92	47	5	28
Mansel 2006	515	516	5	13
McLaughlin 2008	600	336	5	16
B32	2008	1975	8	14

Table I: Lymphedema after SLNB vs ALND in Randomized Trials

Existing studies of LE are complicated by inconsistent relationships in a number of personal, disease, and treatment-related risk factors (26,30). These include having more than five, and in another study 10, positive lymph nodes removed, post-operative infection, radiation to the axilla, younger age at diagnosis, history of hypertension, body mass index > 30 kg/m2 and length of follow-up. The evidence-based risk reduction for breast cancer-related lymphedema is scant and contradictory, with most studies in the area limited by small numbers, retrospective design and other methodological deficiencies. (31) Further, congenital hypoplasia of lymphatics can predispose patients to surgical lymphedema. (32,33) In defining the "functional" anatomy of the axilla by using the methodology of ARM we may be able to not only predict risk, but potentially prevent, lymphedema during SLNB+ALND.

The contribution of radiation to the development of lymphedema in breast cancer patients is highly variable in the literature. For example, in the NCIC MA-20 trial, the incidence of upper extremity lymphedema was 4.5% in patients who were treated with whole breast irradiation (WBI) alone compared to 8.4% with WBI plus regional nodal irradiation (RNI) (p=0.001) (60). In contrast, the contemporary EORTC 22922 trial demonstrated rates of lymphedema of 10.5% versus 12.0% in a comparable cohort (61). It appears that the addition of RNI to breast/chestwall radiation has a greater correlation with lymphedema in the setting of ALND than following SLNB. (62). Thus far, there has been no data published on the interaction of radiation following axillary reverse mapping for breast cancer treatment and limited prospectively collected data on the interaction of the extent of surgical and radiation treatments of the lymphatics.

1.2 Axillary Reverse Mapping (ARM)

Conventional wisdom teaches that the lymphatics reside juxtaposed to the vein, and if the surgeon can avoid skeletonizing the vein, then the risk of lymphedema could be minimized or avoided (Figure 1). If this were the case, then SLNB should have cured the problem of surgical lymphedema. In fact, lymphatics with this positioning are rarely visible or recognized at the time of surgery. Therefore, we hypothesize that lymphedema is related to disruption of virtually unrecognized UE lymphatic drainage during surgery. Földi and others have carefully catalogued the drainage of the various parts of the UE, but once identified as a lymph node in the axilla, lymph nodes are categorized only as axillary lymph nodes not distinguished from where they drain, but by where they are positioned in the axillary bed (e.g. Central).(20, 32) Traditional lymphatic drainage of the UE is based on extensive lymphatic mapping of the UE but not of the axilla.

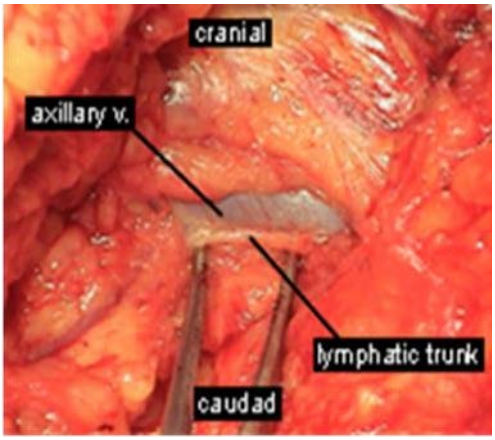

Figure 1. Lymphatic vessel draining the UE is demonstrated just below the Axillary Vein

We developed the concept ARM that utilizes a simple method, namely blue dye injected into the upper volar subcutaneous tissue of the UE to map the lymphatic drainage of the UE in order to determine the *in vivo* anatomical variation in the axillary lymphatics, providing a road map to preserving them (Figure 2). If UE lymphedema is caused by cutting lymphatics, then being able to see and identify them would represent the first surgical procedure designed to preserve them. In effect, ARM is the reverse of SLN mapping that serves to map the lymph nodes draining the breast and then remove them; ARM is mapping the UE drainage in order to preserve it.

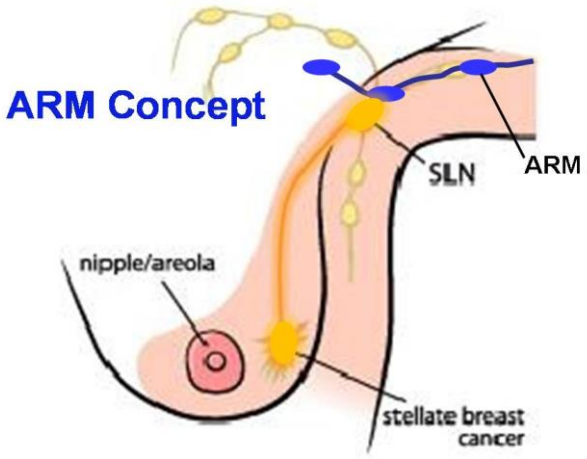

Figure 2 Diagram of Concept of Axillary Reverse Mapping. Radioactive drainage from the breast SLN (yellow) can be identified and removed for examination while the blue lymphatics (ARM) draining the UE can be identified and protected. When the SLN and ARM are the same node, it can be removed and the afferent and efferent lymphatics reapproximated/reanastomosed.

The most significant per person benefit gained by the ARM procedure is in ALND. If ALND is performed after SLNB, the SLNB must also use the ARM procedure as the low-lying lymphatics can otherwise be damaged during the initial staging procedure. A possible drawback to the ARM approach is that at present about half of SLN mapping is done with blue dye or radioactivity alone, and the remaining use dual mapping with both radioactivity and blue dye, especially when learning the technique. In inexperienced hands, dual mapping may be more successful at identifying the SLN. To use ARM, surgeons would have to use radioactivity alone with or without another technique (e.g. magnetic particles) in the breast and reserve the blue dye for the ARM procedure.

The preliminary research focused on the development and safety of the ARM procedure and has demonstrated the ability to identify and preserve the ARM lymphatics in most, but not all, patients and it also showed that there is little crossover (that is that an ARM node is also a SLN) (~4%) between breast and UE lymphatics.(19-24) We have demonstrated safety in a small cohort of patients by removing the ARM identified node during ALND and demonstrating the absence of metastases even in clinically positive axillae. The present study seeks to demonstrate the safety and efficacy of the ARM procedure in preventing lymphedema by comparing lymphedema rates in a large group of patients undergoing axillary lymphadenectomy randomized to with or without ARM.

1.3 Significance of the study

Optimizing breast Cancer Staging:

According to the World Health Organization, as many as 170 million people worldwide and 3-5 million people in the United States suffer from secondary lymphedema. As many and varied procedures have failed to resolve lymphedema, it is our estimation that prevention is the key to avoiding lymphedema and further optimizing breast cancer staging. Axillary Reverse Mapping may be one tool to help us further refine the technique of axillary staging whether performing SLNB and/or ALND. As practiced around the world, the technique of ALND and even SLNB is not standardized, compromising the staging of and recurrence in the axilla and risk of lymphedema. Axillary lymph node dissection does not distinguish breast from UE lymphatics, as the possibility of mapping the drainage from the UE into the axilla has only recently been published by our group and questioned, as well as confirmed, by others using variations of the technique we developed.(19-24,34-41) Transection of the major UE lymphatics during an ALND in patients without significant collaterals most likely is the root cause of lymphedema, arguably the most widely published complication of SLNB or ALND. Some might say the risk from SLNB is low already (0-13%, Table I). However, remember most lymphedema after a SLNB occurs from a negative SLNB. We should strive to lower the risk toward zero of a procedure that ultimately has no benefit to the patient. In addition, the present study may help identify patients who are at risk for LE early on (disrupted lymphatics) and may benefit from early intervention. The ARM procedure is easy to learn and apply. Thus, any surgeon practicing could apply this technique to their present practice of lymphadenectomy with minimal training and cost with a potential huge benefit to the patient in the prevention or mitigation of surgical lymphedema. The preliminary data below outlines the methodical development of expertise in breast cancer surgery, development of SLNB and ARM. Successful completion of the proposed study will help standardize axillary staging and launch a new area in the primary prevention of lymphedema and improvement in overall quality of life. Future studies may use the knowledge gained to determine who is at risk for lymphedema and guide therapeutic surgical interventions for secondary lymphedema.

1.3.1 SLNB reduces LE

As a background to why a new procedure is needed, probe-guided and/or visual resection of radioactive sentinel nodes (the first nodes that receive drainage from tumors) can accurately identify regional metastases in patients with breast cancer. However, multiple studies confirmed this including the definitive NSABP B-32 Trial, which compared LE assessed by volume displacement of SLNB (n=2,006) vs SLNB+ALND (n=1,975) and demonstrated UE volume differences of 7.5% vs 14%, respectively. (18) Many other studies, including the ACOSOG trials, have confirmed that institution of SLNB for breast cancer patients reduces the risk of lymphedema of the affected UE. A recent pooled analysis of 6711 breast cancer patients undergoing SLNB found the incidence of lymphedema to be 6.3% with a range of 0-23%. A similar analysis of 5354 patients undergoing ALND found a pooled incidence of 28% (range 11-57%).(Table I) (42) The literature to date supports injection with blue dye alone, radioactivity alone or in combination.(Reviewed in 43) The best method of injection to localize the SLN remains controversial even today, but a good number of surgeons use subareolar injection.(44) Although beginning surgeons find it easier to use dual mapping and that it may be more accurate, approximately 50% of experienced mappers use single agent localization with high efficacy.

1.3.2 Axillary Reverse Mapping (ARM): A New Concept to Identify and Enhance Lymphatic Preservation

Although SLN clearly reflects the status of the axillary lymph node basin and is less morbid, it has reduced but not prevented lymphedema. We hypothesized that lymphedema may be secondary to disruption of low-lying lymphatics from the UE during a SLNB as well as an ALND. (19-24) After sentinel lymph node localization with subareolar technetium is assured, 5 mL of dermal blue dye was injected in the volar surface of the UE to localize lymphatics draining the UE (axillary reverse mapping, ARM). The SLNB was then performed through an incision in the axilla. Data were collected on identification rates of hot versus blue nodes, variations in UE lymphatic drainage that might impact SLNB, crossover (co-localization) between the hot and the blue lymphatics, and final pathologic nodal diagnosis. Lymphatics draining the UE were near or in the SLN field in 40.6% (87 of 241) of the patients, placing the patient at risk for disruption if not identified and preserved during a SLNB or ALND. ARM demonstrated that UE lymphatics do not co-localize with the SLN drainage of the breast 97.2% of the time and that none of the blue lymph nodes identified by ARM and removed were positive, in this initial study. We identified multiple variations of the UE lymphatics with some being as much as four centimeters below the vein (Figure 3). (21) Some lymphatics identified by ARM were as large as 6 mm. Variations from the traditionally taught position just below the vein were seen as a medial or lateral apron, a sling low in the axilla, blue lymphatics above the vein and a complex of smaller lymphatics entwined as a cord. Lymph nodes identified by ARM were juxtaposed to the hot SLNBs but separable ten percent of the time. Disruption of the blue lymphatics identified by ARM and their close proximity to the hot SLN draining the breast may explain the surprisingly high rate of lymphedema seen after SLNB. A string of inline nodes that drape across the axilla is a rare anatomical finding. Identifying and preserving the blue nodes draining the UE may translate into a lower incidence of lymphedema with SLNB and axillary lymph node dissection.

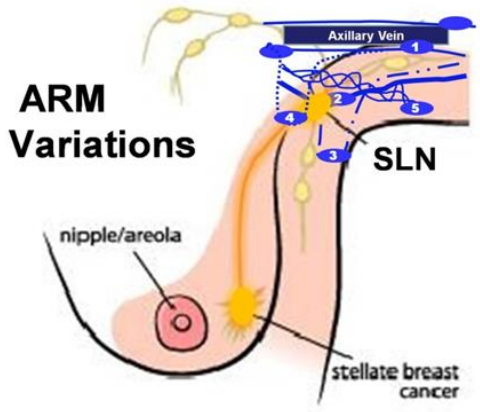

Figure 3 Axillary Reverse Mapping. The diagram demonstrates the anatomical variations in ARM drainage. 1. Lymphatics from the UE running juxtaposed the axillary vein either above or below; 2. Sling low in the axilla; 3. Lateral apron; 4. Medial Apron two consisting of multiple blue nodes; 5. Entwined cord of lymphatics

There have been many small reports, including our original report in 2007, (19) using variable methods for ARM. In the literature to date there are seven studies with >50 patients undergoing ARM (2 ALND only and 5 SNB ± completion ALND) in 859 patients undergoing axillary surgery for breast cancer. Overall, the lymphedema incidence ranged from 0 to 5.7 per cent during ARM-assisted SLNB and 4 to 14 per cent lymphatic preservation during ALND. The SLN co-localized with the blue node identified by ARM in between 0 to 9.6 per cent of patients. Metastases were identified in 0 to 35 percent of these patients. Nodes identified by ARM could not technically be preserved in between 11.1 to 17.5 per cent of patients, metastases were found in 0 to 18.5 per cent of blue nodes from these patients although split mapping was not universally utilized which is important to identify those blue nodes that were also SLNs. All patients where blue nodes identified by ARM were found to be positive were in patients with N3 disease. In our group we are careful to reapproximate/reanastomose afferent and efferent blue lymphatics when blue nodes are

resected. When this is possible we have not seen lymphedema in 20-month follow-up. (45) Of note is that N3 patients would also receive radiation therapy, thus potentially negating chances of recurrence. A randomized controlled trial with adequate follow-up is needed to formally evaluate these outcomes.

In a review of the literature, 4 studies of ARM were assessed at SLNB, but between 10% and 31% of patients went on to undergo a completion ALND. (21, 24, 40, 46) The blue lymphatics or nodes draining the UE were identifiable in between 38% and 100% of patients. Crossover nodes, when the SLN is also the node draining from the UE, were identified in patients undergoing SLNB between 0% and 10% of the time and metastases were present in between 0% and 20% of these nodes as expected as the ARM – identified blue node is the SLN. ARM-identified nodes or lymphatics were sacrificed during ALND in between 0% and 18% of those identified and of those excised the incidence of metastases was between 0% and 18.5%. Low rates of metastases were identified in 1.3 and 4 percent of non-concordant nodes (ARM-identified blue nodes that were not SLNs) in the three studies that reported procedures using ARM as initially reported (split mapping, i.e. radioactivity in the breast and blue dye in the arm). Positive non-concordant blue nodes were only found in patients with heavily positive nodes (N3). (21,24,39) In patients with N3 metastatic disease it is postulated that the lymphatic flow from the breast may back flow into the UE lymphatic drainage and is why split mapping is important to indicate when these nodes should be removed. The reported lymphedema rates were between 0% and 5.4% for ALND when ARM was used. Long-term local recurrence rates were only reported in a single study, (24) which quoted figures of 1.2% and 0.4% for breast and axillary recurrences, respectively. Systemic recurrence was quoted as 6.4% overall.

The remaining study (Kuusk et al) divided patients into SLNB alone and ALND alone patients. (47) This study identified nodes or lymphatics draining the UE in 27% of patients. Crossover nodes were present in 9.6% (5 patients) of patients SLNs and metastases were present in one (20%) of these which is what one would expect for a SLN positivity rate. Overall, 14.2% of ARM-identified lymphatics were sacrificed, with no involved nodes identified and an incidence of lymphedema of 5.7% with no recurrences. In the 2 studies, which performed blue dye injection of the UE without breast injection in 203 consecutive breast cancer patients scheduled to undergo ALND alone (22, 36), blue lymphatics or nodes were identified in 78.3% and 100% of occasions. The preservation of blue lymphatics was possible in 52.6% and 75% of cases. The lymphedema rates ranged between 9% and 23% in the blue lymphatic preservation groups and between 33.3% and 40% in the non-lymphatic preservation sacrifice group. There were no reported cases of local recurrence. (48,49) Further, Yue and colleagues performed a randomized study in 265 patients undergoing ALND randomized to arm lymphatic mapping but without breast injection) versus ALND only. In the control group 33% developed lymphedema and 6% in the patients with UE lymphatic mapping at 20-month follow-up. (50) FNA was performed on blue nodes and they were removed if positive. This occurred in 8.5% of the patients. This study demonstrates the necessity to perform concurrent radioactivity in the breast as well as blue dye in the UE as it has been shown that 4 to 6% (~half) of these nodes are SLNs and thus a high nodal positivity and as such should be removed. No nodal recurrences were seen during follow-up.

In follow-up data in a single institution prospective trial 642 patients have undergone 685 ARM procedures with a SLNB and/or ALND (45) Objective lymphedema rates by volume displacement for SLNB and ALND were 0.8% and 6.5%, respectively, with 26-month median follow-up. Blue lymphatics were identified in 29.2% (138/472) of SLNB and 71.8% (153/213) of ALND. Crossover was seen in 3.8% (18/472) of SLN and 5.6%

(12/213) of ALND. Blue node metastases rate was 4.5% (2/44) both in N3 disease. Axillary recurrence rate was 0.2% and 1.4% for SLNB and ALND, respectively.

1.3.3 Lymphatic Re-anastomosis

A total of 81 blue ARM-identified blue lymphatic transections occurred during a single institution study; thirty-one instances during SLNB and 50 during ALND. Of the 31 patients where blue lymphatic injury was identified at the time of SLNB, 15 (48.3%) had a lymphatic reanastomosis/reapproximation performed. An additional 18 patients out of 50 (36%) had similar re-anastomosis of blue lymphatics during ALND. Consistent reapproximation of lymphatics only occurred starting in 2011. In the subset of patients in which an identified blue lymphatic was transected, there was an overall lymphedema rate of 18.7% (9/48) when not reanastomosed/reapproximated, and 0% (0/33) when re-anastomosed/reapproximated (p=0.009); this is over an average follow-up of 20 months (range 3-54 months).

1.4 Hypothesis and study objectives

We hypothesize that mapping and sparing the lymphatics draining the UE during SLNB or ALND would decrease the subsequent development of lymphedema as compared to SLNB or ALND without sparing the UE lymphatics. Variations in anatomic location of the lymphatic drainage of the upper extremity within the axilla put the lymphatics draining the UE at risk for disruption during a SLNB and /or ALND. Therefore, mapping and protecting the drainage of the UE versus that of the breast within the axilla using blue dye to identify and protect the lymphatics draining from the UE (ARM) and radioactivity to map those draining from the breast in order to stage it would decrease the likelihood of inadvertent disruption during lymphadenectomy reapproximation/reanastomosis when disrupted and thus reduce the risk of subsequent lymphedema.

1.5 Study methods and study design

In this prospective randomized Phase III trial, patients with non-inflammatory breast cancer, two cohorts of patients with non-inflammatory breast cancer are planned for enrollment. Cohort I will include clinically node negative infiltrating mammary cancer desiring a mastectomy and lymph node staging will be randomly assigned to Group I (SLN mapped with technetium alone and/or with blue dye) or Group II (SLN mapped with technetium alone and ARM performed with blue dye alone). Patients with positive sentinel nodes at surgery within each group will undergo ALND. Group I+ALND will undergo standard ALND without further injection. Group II+ALND will undergo standard ALND at an initial or second operation. If the ALND is not performed at the initial setting, then blue dye for ARM will be re-injected at the time of the second surgery for identification of blue lymphatics taking care to spare or re-approximate the blue ARM-identified lymphatics. Cohort II will include patients with clinically positive nodes undergoing either mastectomy or breast conserving surgery (BCS) and are additionally undergoing an ALND. Patients in cohort II will similarly be randomized to Group I or Group II, no ARM vs ARM respectively in conjunction with ALND.

2.0 OBJECTIVES

2.1 Primary objective

To determine the occurrence of post-surgery lymphedema by conical geometric measures in clinical T1-3, N0-3, M0 breast cancer patients undergoing axillary surgery and randomized to Group 1 (no ARM) versus Group II (ARM).

2.2 Secondary objectives

2.2.1 To compare between the study groups the lymphedema symptom intensity and distress as measured by the Lymphedema Symptom Intensity and Distress Survey-Arm (LSIDS-A).

2.2.2 To evaluate the technical success of performance of ARM procedure: Identification of ARM lymphatics, and the ability to spare or reapproximate ARM lymphatics.

2.2.3 To compare the rate of regional recurrence between patients randomized to receive ARM versus no ARM.

2.3 Exploratory objective

2.3.1 To assess the occurrence of lymphedema as a function of radiotherapy use and targets.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease that, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.2.1 Documentation of Disease:** cT1-3 patients undergoing axillary surgery who additionally meet one of the following conditions:

1. Clinically node negative patients undergoing mastectomy and SLNB with possible ALND if SLNB is positive. If ALND is performed during a separate operation, ARM procedure must be repeated. Clinically node negative is defined by i) negative clinical exam and/or ii) negative axillary US and/or iii) negative needle biopsy of sonographically suspicious axillary nodes as applicable to each case.

2. Clinically node positive patients as determined by needle biopsy and planned for ALND regardless of type of breast surgery.

Patients will be staged according to the TNM staging system.

___ **3.2.2 Prior Treatment:** No prior axillary surgery on the ipsilateral side except needle biopsy or concurrent SLNB.

Prior neoadjuvant chemotherapy is allowed but must be completed at least 2 weeks before registration.

___ **3.2.3 No prior history of ipsilateral breast cancer** (invasive or DCIS). LCIS and benign disease are allowed. (May have neoadjuvant chemotherapy which must be completed 2 weeks before registration).

___ **3.2.4 No bilateral invasive breast cancer**

___ **3.2.5 No matted nodes (by clinical exam)**

___ **3.2.6 No history of lymphedema of either arm**

___ **3.2.7 No known allergies blue dyes, including make-up containing blue dye**

___ **3.2.8 In order to complete the mandatory patient-completed measures, participants must be able to speak and/or read English.**

___ **3.2.9 Female**

Men are excluded from this study because the number of men with breast cancer is insufficient to provide a statistical basis for assessment of effects in this subpopulation of people with breast cancer.

___ **3.2.10 Age ≥ 18 years**

___ **3.2.11 ECOG Performance Status 0, 1 or 2.**

___ **3.2.12 Required initial Laboratory Values:**

Creatinine: ≤ 1.5 x upper limit of normal (ULN)

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at [redacted] In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at [redacted]

RCR utilizes five person registration types.

- **IVR**—MD, DO, or international equivalent;
- **NPIVR**—advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- **AP**—clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave; acting as a primary site contact, or with consenting privileges
- **Associate (A)—**other clinical site staff involved in the conduct of NCI-sponsored trials; and
- **Associate Basic (AB)**—individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at [redacted] For questions, please contact the **RCR Help Desk** by email at [redacted]

4.2 CTSU Site Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling [redacted]

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
  - Active status at the site(s) on the IRB/REB approval on at least one participating organization's roster;
  - If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
  - Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
  - Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

4.2.1 Additional site registration requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);

- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.2 Protocol specific requirements for A221702 Site Registration

IROC credentialing:

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at [redacted]Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU website.

IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.

Surgical credentialing approval:

See Section 14.0 for further instructions. Surgeons participating on this trial must be rostered at the enrolling site because the primary endpoint of the trial is related to surgical outcomes.

4.2.3 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website[redacted] using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number [*A221702*].
- Click on *Documents*, *Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.4 Submitting Regulatory Requirements

Submit required forms and documents to the CTSU Regulatory Office using the *Regulatory* Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] in order to receive further instruction and support.

4.2.5 Checking Your Site's Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.2.6 Credentialing

See Section 14.0 for credentialing requirements.

4.3 Patient Registration Requirements

Informed consent: The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patient completed booklets: Patient-completed booklets should be downloaded prior to the registration of any patients. These booklets can be downloaded from the CIRB Approved Documents tab on the CTSU website. Patient-completed booklets will only be available in English. .

4.4 Patient Registration/Randomization Procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN Corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).
- Surgical credentialing is complete, and approval has been obtained as per instructions in Section 14.0 of the protocol.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted] For any additional questions, contact the CTSU Help Desk at [redacted]

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol-specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

4.5 Stratification Factors and Treatment Assignments

All eligible subjects will be randomized, using permuted block of size 4 or 6, separately by planned surgery type.

Grouping Factors: Mastectomy versus Breast Conserving Surgery

With stratification by:

4.5.1 Clinical tumor size (at the time of initial diagnosis):

≤ 2.0 cm vs > 2.1 cm

4.5.2 Clinically positive axillary nodes:

yes vs. no

4.5.3 BMI:

≥ 30 versus < 30

5.0 STUDY CALENDAR

Pre-Study Testing Intervals: The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

To be completed ≤ 30 DAYS before registration: All laboratory studies, history and physical.

To be completed ≤ 60 DAYS before registration (except for patients who received neo-adjuvant chemotherapy): Baseline exams, mammograms or axillary ultrasound¥ utilized for documentation of diagnosis.

	Prior to Registration	Within 30 days prior to Surgery	30 days following Surgery*	Post treatment follow up at 12, 24 and 36 months **
Tests & Observations:				
History and physical, weight, PS	X		X	X
Pulse, Blood Pressure	X			X
Adverse Event Assessment		X	X	X
Clinical Lymphedema assessment		A		A
Arm Circumference measure (see Section 11.1 and Appendix I)		X		X
Laboratory Studies:				
Serum or Urine HCG		B		
Serum Creatinine	X			
Clinical Staging:				
Mammogram and Axillary Ultrasound ¥	X			
Recurrence Evaluation				X
Questionnaires:				
LSIDS-A		X		X

* +/- 2 weeks

** +/- 3 months for all follow-up assessments.

A To be assessed per the CTCAE criteria.

B For women of childbearing potential. Must be done ≤ 7 days prior to surgery. Patients who become pregnant prior to surgery must discontinue protocol treatment (See Section 12.2).

¥ Breast MRI may be used instead of mammogram and axillary ultrasound as imaging.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule:

A Schedule of Forms is available on the Alliance study webpage, within the Case Report Forms section. The Schedule of Forms is also available on the CTSU site within the study-specific Education and Promotion folder, and is named Time & Events.

6.1.2 Medidata Rave

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to [redacted] for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management > Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management

> Rave section at [redacted] or by contacting the CTSU Help Desk at [redacted] or by email at [redacted].

Patient-completed questionnaire booklets for this study should be downloaded prior to the registration of any patients (see Section 4.3). These booklets can be downloaded from the CIRB Approved Documents tab on the CTSU website. Booklets must be given to patients to complete, and patients should be instructed to return the booklets/responses to site staff (either in person, by mail, by email, or by phone), and site staff will enter patient responses into Rave. Patient-completed booklets will only be available in English.

Verbal administration of the measures for visually impaired patients is permitted if the measure and verbal administration of the measure is conducted in a language understandable to the patients.

6.1.3 Data Quality Portal:

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

6.1.4 Supporting Documentation to be submitted to the Alliance

This study requires supporting documentation for diagnosis, surgery and recurrence. Supporting documentation will include, pathology, radiology, surgery- reports, etc. These must be submitted accordingly:

- Pathology report of diagnosis: At registration
- Pathology Report from operative procedure
- Operative notes
- Pathology Report of any documented axillary recurrence

Supporting documentation is to be submitted via Rave.

6.2 Digital radiation therapy data submission using Transfer of Images and Data (TRIAD)

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

6.2.1 TRIAD Access Requirements

- A valid Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) (CTEP-IAM) account.
- Registration and Credential Repository (RCR) registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR) registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

6.2.2 TRIAD Installations

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at [redacted]

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email [redacted]

Data to be submitted is detailed in Section 7.4.4.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 60 days of registration.

For questions regarding treatment, please see the study contacts page.

If there is a second staged surgery, it must be completed within 60 days of first operation or within 90 days after planned adjuvant therapy.

7.1 Surgery

It is expected that surgery will be performed at the registering institution. Each patient will receive an injection of up to 1.0 mCi of technetium-99m sulfur colloid into the normal breast tissue surrounding the primary cancer or biopsy cavity directed subareolar or around the tumor and/or dermally. The material will be prepared as per manufacturer's specifications for injection. Using saline as a diluent, the final volume will be 4.0 ml or less. In the case of a patient with clinically negative nodes that the technetium does not locate the SLN ex vivo, the surgeon will be allowed to use blue dye in the breast in order to locate the SLN. In such a case the surgeon will not perform the ARM procedure. Other techniques may be added to radioactive localization of the breast SLN (e.g. magnetic particles).

After localization of the SLN the isosulfan blue dye may be injected into the breast in Group I. In Group II it will be injected subcutaneously in the volar surface of the ipsilateral UE in order to locate the draining lymphatics from the UE. No more than 5cc of blue dye will be injected. Site of all injections (radioactivity and/or blue dye) is to be recorded.

Using gamma probe technique, a sentinel lymph node biopsy will be performed in patients with clinically negative nodes (Schema I). Patients with positive nodes within each group may undergo a Level I and II ALND. Group I+ALND will undergo standard ALND without further injection. Group II+ALND will undergo standard ALND+ARM at an initial or second operation. If the ALND is not performed at the initial setting then blue dye for ARM will be re-injected at the time of the second surgery for identification of blue lymphatics, taking care to spare or re-approximate the blue lymphatics draining the UE. When an ALND is planned without SLN biopsy, then it is important to inject the radioactivity in the breast to map the drainage of the breast and determine if the blue node draining the arm is also the hot node draining the breast. If this is the case, the blue node should be excised because of the increased risk of crossover from the breast and nodal positivity and sent to pathology separately; in this situation, afferent and efferent lymphatics should be reapproximated. The surgeon may remove the blue node if there is any suspicion of positivity or concern and again reapproximate.

Definition of Sentinel Lymph Node Biopsy: A minimum of 1 sentinel node and a maximum of 6 total nodes (sentinel + non-sentinel) are identified and excised by the surgeon.

Definition of positive nodes: At least one lymph node (sentinel or non-sentinel) with a metastasis greater than 0.2 mm in greatest dimension identified on intra-operative pathologic assessment.

Note: Isolated tumor cells (metastases less than or equal to 0.2 mm) will be treated as node negative disease (N0i+).

7.1.1 Surgical Quality Assurance

This protocol requires training in the ARM procedure. See Section 14.0 for credentialing requirements.

If a deviation should occur, the patient should continue to be followed per protocol.

The following quality measures will be continually assessed throughout the trial enrollment period, on a per surgeon and per institution basis. Sites with persistent data reflecting poor surgical quality by the metrics outlined below will be unable to continue enrollment in this study.

7.1.2 Definitions of Deviations in Protocol Performance

Major Deviations:

a) Axillary procedures

1. Not removing cross over nodes
2. Going straight to node dissection in clinically node negative patients except in the case of non-localization of the SLNB.
3. Not following the procedure designated by the group you were randomized by error.
4. Removing more than 6 nodes total (sentinel + non-sentinel) for a sentinel lymph node biopsy
5. For patients undergoing ALND, less than 10 nodes, if no neoadjuvant chemotherapy (NAC) received, or less than 8 nodes, if NAC received, will be considered a major deviation. These node counts include nodes harvested as part of sentinel node biopsy.

b) Breast procedures

1. Failure to achieve negative margins should be achieved prior to proceeding on to adjuvant radiation therapy. Negative margins are defined as no (DCIS or invasive) tumor on ink.

Minor Deviations:

a) Axillary procedures

1. Failure to attempt to reanastamose afferent and efferent lymphatics after resection of cross over node
2. Failure to inject isotope and look for cross over node
3. Lack of description of intraoperative findings, anatomy, procedure
4. For patients undergoing ALND, failure to meet these criteria would be considered a minor protocol deviation.
    - Identification and preservation of and noted in operative report:
    - Axillary vein
    - Long thoracic nerve
    - Thoracodorsal nerve

• Complete level I and Level II axillary dissection (with or without level III dissection at the treating surgeon's discretion

b) Breast surgery

1. The site of the initial biopsy proven breast cancer should be proven to have been resected (by either lumpectomy or mastectomy). Methods to prove that the initial biopsy proven site has been resected include any or all of the following:

- Clip placed at the site of initial cancer documented in the specimen with a specimen radiograph (x-ray of the resected surgical specimen).
- Clip placed at site of initial cancer identified by pathology in the resected surgical specimen.
- Biopsy site changes OR residual tumor OR therapy effect noted on pathology report from surgical specimen.

Note: In cases with more than 1 focus of biopsy proven cancer, documentation of resection of all sites of biopsy proven disease is required.

7.2 Chemotherapy/ Systemic therapy

Any adjuvant hormonal therapy is allowed. It may begin any time relative to the radiation, at the discretion of the treating physician.

Chemotherapy is allowed. If adjuvant chemotherapy is indicated, it can be delivered before or after radiation therapy. Neoadjuvant chemotherapy is allowed but must be completed at least 2 weeks before registration.

Cytotoxic systemic therapy may not be used concurrently with radiation. However, trastuzumab, pertuzumab or other biological therapy may be given concurrently per standard of care.

After finishing cytotoxic chemotherapy, a minimum of 21 days must elapse before the start of radiation. If cytotoxic chemotherapy is started after radiation, a minimum of 21 days must pass after the last fraction of radiation before beginning chemotherapy.

7.3 Radiotherapy

Adjuvant radiation therapy is allowed. Radiation therapy may be administered at external radiation therapy facilities, if they meet the requirements outlined in Section 7.5. Standard or hypofractionated radiation as outlined are both allowed on study.

In those undergoing radiation therapy, treatment planning should begin after consultation with the radiation oncologist. Radiation therapy should ideally begin no earlier than 3 weeks (21 days) following surgery. Timing starts after the last surgery performed for local control (i.e. if a patient requires a second or third operation to achieve negative margins or for ALND; ideally, it is recommended that radiation therapy should begin between 3 weeks and 12 weeks after the last surgical procedure.) Patients may be treated with 3DCRT, IMRT or proton beam.

See Section 14.1 for the credentialing requirements for this study.

Unacceptable deviations will be scored for failure to prescribe proper dose and not treating the required regional lymph nodes, including internal mammary lymph nodes, if indicated as outlined in Sections 7.3.2 and 7.3.3.

Every attempt should be made to meet dose constraints. If dose constraints are not met, patients will remain on protocol treatment unless in unusual circumstances it is recommended that they

be removed from protocol treatment by a radiation co-chair. It is recommended this be discussed with a radiation co-chair prior to starting radiation.

All radiation therapy questions should be directed to the Alliance A221702 Radiation Co-Chairs. (see cover page)

The radiation contouring parameters are adapted from RTOG criteria, as outlined in the RTOG breast atlas: [redacted]

7.3.1 Selection of Patients for radiation therapy:

Post mastectomy radiation is recommended to be given by the treating radiation oncologist utilizing the following guidelines:

- pT3N1-3
- pT1-2N2-3
- ypN1-3 (any positive lymph node disease following neoadjuvant chemotherapy)
- cN2-N3ypN0
- pT1-2N1, pT3N0, cN1ypN0 per discretion of the treating provider.

Post conservative breast surgery radiation is recommended to be given by the treating radiation oncologist utilizing the following guidelines:

- All patients will undergo whole breast radiation
- For patients receiving regional radiotherapy/ regional nodal irradiation the dose constraints for Alliance A221505 and MA.39 are recommended, as outlined below:
    - pT3N1-N3
    - pT1-2N2-3
    - cN2-3ypN0
    - ypN1-3 (any positive lymph node disease following neoadjuvant chemotherapy)
    - pT1-2N1, pT3N0, cN1ypN0 per discretion of the treating provider

7.3.2. Radiation targets:

For those patients requiring radiation as outlined above, radiation will be delivered to the following planning targets. Post mastectomy radiation will target: the chest wall undissected axilla, * supraclavicular nodes and internal mammary nodes in the first 3 intercostal spaces. Post conservative breast surgery radiation will target: the breast and if indicated as outlined above, the regional lymph nodes: undissected axilla,* supraclavicular nodes, and internal mammary nodes in the first 3 intercostal spaces.

*The undissected axilla will vary depending on the extent of surgical removal of lymph nodes as per the below:

- If a sentinel lymph node biopsy +/- ARM is performed, then the level I-III axilla are included.
- If an axillary lymph node dissection is performed, then the level of the axilla targeted for radiation will be determined based on a review of the surgeon's operative report and pathology specimen.
- If the level I axilla is dissected, then levels II-III of the axilla should be targeted.
- If the level I-II axilla are dissected, then level III of the axilla should be targeted.

- If the level I-III axilla are dissected, then none of the axillary lymph nodes should be targeted
- If the dissected axilla has a high residual tumor burden as defined by >50% of dissected lymph nodes being involved with tumor plus the presence of extracapsular extension, then the Level I and II axilla may be targeted.

The supraclavicular field lateral border is typically at the coracoid process or medial aspect of the humeral head, but can be extended laterally if necessary to cover the full axilla at the discretion of the radiation oncologist with or without a posterior axillary boost field for patients with a high residual disease burden in the dissected axilla.

7.3.3 Dose specifications

Chest wall

50 Gy in 2 Gy daily fractions over 5-6 weeks or 42.56 Gy in 2.66 Gy daily fractions over 16 fractions. Boost: boost to the chest wall/scar using standard fractionation of 10-14 Gy in 2Gy daily fractions or for hypofractionation: 10-12.5Gy in 2.5Gy daily fractions. The boost is optional for all post mastectomy patients. This is generally performed with electrons though other techniques may be employed provided they adequately cover the Planning Target Volume (PTV) Evaluation as described. The use of skin bolus is often recommended for post-mastectomy irradiation, but ultimately is per the treating physician's discretion to individualize to the patient's treatment and radiotherapy plan. If using bolus, the skin dose should follow the same constraints as the Chest wall PTV Evaluation.

Regional Nodal Irradiation

Undissected axilla, supraclavicular nodes, and internal mammary nodes: 50 Gy in 2 Gy daily fractions over 5 weeks or 42.56Gy in 2.66 Gy daily fractions over 16 fractions. In patients treated with an axillary dissection the dose to the supraclavicular and axillary nodes can be reduced (for conventional fractionation: 45 Gy in 25 fractions; and for hypofractionation: 40 Gy in 16 fractions).

Whole Breast Irradiation

If radiation is delivered to the breast alone with no regional nodal irradiation, the dose to the whole breast will be 42.56Gy/16 fractions or 50.00 Gy/25 fractions. If regional nodal irradiation is given together with whole breast radiation, then the whole breast dose will be 50 Gy in 2 Gy daily fractions over 25 fractions or 42.56 Gy in 2.66 Gy fractions over 16 fractions. Boost: an optional boost to the lumpectomy cavity of 10-14 Gy in 2Gy fractions if using conventional fractionation and 10-12.5 Gy in 2.5 Gy fractions may be given. Skin bolus is not allowed on the intact breast.

Proton dose specification

If proton radiation is used in treatment, the dose values are all referred to the relative biological effectiveness (RBE) weighted absorbed dose, which is the product of the RBE and absorbed dose. The value of RBE is taken as 1.10 with respect to Cobalt-60 throughout the treatment volume.

7.3.4 Technical factors

3-dimentional CT based treatment planning is required.

Calculations shall take into account the effect of tissue heterogeneities. When protons are used, tissue heterogeneity calculations should be performed with a CT-based treatment planning system to generate dose distributions from the proton relative stopping power.

Use of IMRT is allowed. Please see the section below entitled IMRT regarding guidelines.

Proton Radiation Therapy (PRT) is allowed, including both passive scattering and active scanning proton delivery techniques, provided they have been credentialed by the IROC Houston QA Center.

Linear accelerators with a minimum photon energy of 6MV are required for photon treatment.

Either photons and/or electrons may be used for boost treatment.

Localization, simulation and immobilization

Simulation and treatment must be performed with the patient in the supine position for postmastectomy radiation and whole breast plus regional nodal radiation. The prone position may be used for patients undergoing whole breast radiation alone. Patients should be optimally positioned with alpha cradle casts, vac fix, breast boards, wing boards, and/or other methods of immobilization at the discretion of the treatment physician.

Methods to minimize the cardiac exposure to RT like heart block, gating or breathhold are allowed at the discretion of the treating physician.

For large-breasted patients, including those with a large inframammary skin fold, devices to improve positioning of the breast are permissible.

A treatment planning CT scan in the treatment position will be required to define the clinical target volumes (CTV), planning target volumes (PTV) and Organs at Risk (OAR).

The treatment planning CT must be post final surgery, either lumpectomy or mastectomy, as well as post final axillary surgery.

For post-mastectomy patients (Schema I): radio-opaque markers are to be placed on the patient's skin in the treatment position as external landmarks at the acquisition of the CT scan to facilitate contouring segmentation of the CT data-set. These markers should identify: 1) the mastectomy scar, and 2) the clinical outline at least from 2 o'clock to 10 o'clock of the "at risk" chestwall representing where the breast previously was located.

For patients that have an expander in place post-mastectomy for reconstruction, the amount of expansion before radiation is per the treating physician's discretion. The position of the expander, ranging from collapsed to fully expanded, that is present at the time of acquisition of the CT scan for treatment planning must remain stable until the completion of radiotherapy.

For post-conservative breast surgery patients (Schema II): radio-opaque markers are to be placed on the patient's skin in the treatment position as external landmarks at the acquisition of the CT scan to facilitate contouring segmentation of the CT data-set. These markers should identify: 1) the lumpectomy incision, 2) the outline of the palpable breast tissue circumferentially at least from 2 o'clock to 10 o'clock, and 3) the superior border of the breast tissue at 12 o'clock based on palpation. Additional markers to define the borders of "clinical" tangent fields (e.g., based on the palpable breast tissue and boney landmarks) are often helpful.

The CT scan should extend cephalad to start at or above the mandible and extend sufficiently caudally (or inferiorly) to the inframammary fold to encompass the entire lung volume. A CT scan image thickness of ≤ 0.5cm should be employed.

External skin localizing marks, which may include permanent tattoos, are recommended for radiation daily localization and set-up accuracy.

Each of the following volumes and normal structures must be delineated on each slice of the planning CT:

Post Mastectomy Volumes: Chestwall, undissected axilla (as defined in Section 7.3.2), supraclavicular and internal mammary nodes in the first 3 intercostal spaces as defined in the RTOG Breast Atlas and below.

Post Conservative Breast Surgery Volumes if targeting whole breast alone: Breast, lumpectomy

Post Conservative Breast Surgery Volumes if targeting whole breast plus regional lymph nodes: Breast, lumpectomy cavity, undissected axilla (as defined in Section 7.3.2), supraclavicular and internal mammary nodes in the first 3 intercostal spaces as defined in the RTOG Breast Atlas and below.

Normal Tissue: right and left lung, contralateral breast, heart, thyroid.

Normal tissues should be delineated as follows

Contralateral breast: Includes the apparent CT glandular breast tissue visualized by CT and consensus definitions of anatomical borders from the RTOG Breast Atlas. In general the borders are:

Posterior border: at the anterior surface of the pectoralis, serratus anterior muscles, excluding chestwall, ribs, boney thorax and lung/heart

Medial border: the sternal-costal junction

Lateral border: varies based on the size of the breast, but typically is at the mid-axillary line and excludes the ipsilateral latissimus dorsi muscle.

Cephalad border: should be similar to that of the ipsilateral breast CTV

Anterior border: skin minus 5mm to minimize inaccuracy of dose calculations at the skin surface.

Ipsilateral and contralateral lung: These may be contoured with auto-segmentation with manual verification.

Heart: This is to be contoured on all cases (not just left sided cases). The heart should be contoured beginning just inferior to the level in which the pulmonary trunk branches into the left and right pulmonary arteries (PA). Above the pa, none of the heart's 4 chambers are present. The heart should be contoured on every contiguous slice thereafter to its inferior most extent near the diaphragm. The following structures, if identifiable, should be excluded from the heart contour: esophagus, great vessels (ascending and descending aorta, inferior vena cava). One need not include pericardial fat, if present. Contouring along the pericardium itself, when visible, is appropriate.

Thyroid: The thyroid is easily visible on a non-contrast CT due to its preferential absorption of iodine, rendering it "brighter" or denser than the surrounding neck soft tissues. The left and right lobes of the thyroid are somewhat triangular in shape and often do not converge anteriorly at mid-line. All "bright" thyroid tissue should be contoured.

IMRT

The following definitions and conditions are applied concerning IMRT in this protocol:

1) The treatment plan will be considered IMRT for the purposes of this protocol if an inverse planned optimization is used to determine the beam weights to meet the target and critical structure dose-volume constraints.

2) A plan generated by direct aperture optimization that employs an inverse planning algorithm is considered as IMRT when the target and critical structure dose-volume constraints are met and at least 3 apertures for each beam direction are used.

3) If IMRT is combined with the standard open medial and lateral tangential fields for whole breast irradiation, the IMRT beam, as described in number 1) above, should deliver > 50% of the total number of monitor units for the beam orientation.

4) If an IMRT plan is used with another IMRT plan, forward-planning photon beams, and/or electron beam, the composite dose distribution and DVHs should be generated.

5) All standard IMRT planning and delivery systems using MLC (step-and-shoot, dynamic MLC, slide-and shoot, VMAT, tomotherapy) are allowed and classified as IMRT as long as target and critical structure dose-volume constraints are met.

6) IMRT planning and delivery systems using physical beam-intensity compensators designed by an inverse algorithm to modulate beam intensity so that the required dose constraints are met are also accepted as IMRT.

7) The patient specific pre-treatment QA measurement is required prior to the first treatment for an IMRT plan.

All plans that do not fit into the above definitions and conditions are classified as 3DCRT plans. Specifically:

The plans generated using forward-planning methods or segmental techniques such as "field-in-field" to meet dose-volume constraints are considered as 3DCRT plans. These forward-planned or segmental treatment techniques are those intended mainly to improve the uniformity of the dose distribution, but not to produce steep dose gradients to protect critical structures (e.g. heart or lung).

The plans with the number of apertures < 3 for each beam direction are considered 3DCRT plans even if they were generated with inverse planning algorithms.

Proton Therapy

Proton treatment by techniques of passive scattering (PS), uniform scanning (US) and pencil beam scanning (PBS) are all permitted provided the site has been appropriately credentialed by IROC Houston for the technique they are using.

Basic treatment planning guidelines are as follows:

1. A conventional proton RBE value of 1.1 shall be used for planning.
2. The radiopaque markers placed on patient during CT simulation should be excluded from the body surface contours or have their proton stopping power ratio

(SPR) reset to that of air so that they are not considered in dose calculations. Inclusion of such markers in the dose calculation will result in overshooting.

3. In the presence of breast implant(s), volumes must be contoured with proton SPR reset to a value for the specific material used in the implant(s). Such values can be obtained by measurement or from the literature. CT scans with orthopedic metal artifact reduction (MAR/OMAR/IMAR) may be used if available to reduce the streaking artifacts due to the metal tissue expander. If metal artifact reduction is not available, it is suggested that image fusion between kVCT and MVCT be used to remove the artifacts in the planning kVCT.
4. Field arrangement is at the discretion of the treating physician; however, at least two fields are recommended to reduce the skin dose for passive scattering (PS), uniform scattering (US). In PBS, the skin dose may be mitigated through intensity modulation.
5. Multiple fields with multiple isocenters and/or multiple gantry angles may need to be used to cover large target volumes or to improve dose homogeneity across the target volume, e.g., for PS or US. In such cases, the matchline may be feathered. Multiple fields may also be needed for certain PBS systems with a small field size limit (e.g., single room systems). In those cases, the technique of tapered dose distribution (edge smoothing or gradient optimization) at the field matchline must be used to reduce dose heterogeneity due to matchline shifts during field switching.
6. For PS and US beams, the perturbation of the proton dose distribution due to misalignment of the compensator and the anatomy may be compensated by applying smearing to the compensator. The smearing radius will be calculated using the algorithms established at each participating institution. The compensator may be smoothed to reduce hot spots and dose gradient from target volume to aperture edge. A block margin must be assigned depending on the penumbra specific to the proton beam being used. Note that proton beam penumbra is a function of proton energy and the airgap between the distal surface of the compensator and the patient's skin surface. It may vary significantly from one clinical situation to another. The definition of airgap also varies from one treatment planning system to another.
7. The treatment planning parameters, including distal and proximal margins, airgap, block margin, and the smearing radius may be modified for the local machine characteristics and practice. Variation of magnitudes in these parameters from one institution to another is acceptable; however, the parameters selected must ensure specified target coverage and normal tissue sparing in the face of range and set up uncertainties.
8. For PBS beams, a range shifter (specific for each institution) is used to produce spot positions more shallow than those delivered by an institution's lowest available energy. Note: the airgap chosen for each field together with the range shifter increase the spot size.
9. Placement of beam spots in the planes perpendicular to the beam direction and the number of spot layers used along the beam direction may vary from one institution to another with spot scanning beams.
10. Plan robustness against geometric targeting uncertainty: For PS or US, proper aperture margin and compensator smearing per local institutional guidelines should be consistent with the setup uncertainty for the specific setup technique and

equipment used at the center for this type of treatment. For PBS, optimization volumes with margins sufficient to ensure target coverage or a robust optimization algorithm may be used to achieve coverage robustness. Robustness evaluations of each patient's plan are recommended.

11. Plan robustness against range uncertainty: For PS or US, the general practice is to add an additional 3.5% of the maximum beam range + 3 mm to the beam range calculated based on the water equivalent path lengthy (WEPL) to the most distal point of the target volume, which is beam specific. Note that the 3.5% increase should be applied only to the portion of the beam passing through the patient's tissue, which is the only source of the uncertainty. For example, the WEPL value of a range shifter, if in use, must be subtracted from the beam range before the 3.5% ratio is applied. Another example where caution may be exercised is the rare occasion when the chestwall and the supraclav/axilla nodal targets can all be included by a single PS field in a postmastectomy treatment. The chestwall portion of the target volume is only 2-3cm thick, while the axilla nodal regions could be much deeper, requiring larger beam range. In this case, directly applying the 3.5% + 3 mm to the total beam range may result in unnecessary overshooting in the chestwall. For PBS, field specific target volume with the expansion in the longitudinal direction commensurate with the range uncertainty may be used.
12. It is recommended that PBS optimization should include the skin (up to 5mm inner rind from the external contour) as an OAR.

7.3.5 Treatment planning

The goals of treatment planning in this study are to encompass the chest wall/breast targets and nodal PTVs (when targeted, as outlined above), and minimize inclusion of the heart and lung. Detailed dose volume histogram-based target planning goals are delineated below.

Field arrangements for 3D conformal, IMRT and PRT of the chest wall/breast and nodal PTVs are defined below with some discretion of the treating physician. Multiple beam arrangements are to be designed during the treatment planning process to produce an optimal plan that meets the dose-volume constraints on the target volumes and normal tissues outlined below.

Treatment plans must meet Dose Volume Constraints for the contoured targets and normal structures. Various treatment approaches may be used to develop treatment plans.

Standard tumor and target volume definitions

International Commission on Radiation Units and Measurements (ICRU) Reports 50, 62 and 78 ([redacted]) define prescription methods and nomenclature that will be utilized for this study. Treatment planning will be based on the following definitions:

Gross tumor volume (GTV) is the volume occupied at diagnosis by visible or palpable disease.

Clinical target volume (CTV) includes the GTV and sites with potential occult tumor involvement including lymph nodes adjacent to the GTV that may be clinically involved.

Planning target volume (PTV) is the CTV surrounded by a geometric margin to account for variability in set-up, breathing or motion during treatment.

The PTV will be uniquely defined for proton therapy and will include a margin which is added to the CTV in 3-dimensions. The margin should be consistent with the motion

control and setup accuracy for the particular type of treatment (scattered versus scanning) at the treating proton center.

When proton therapy is used, the PTV will be used for dose reporting and not specifically for treatment planning. The goal of treatment planning will be CTV coverage at 100% with measures taken for each specific uncertainty.

For proton therapy, the PTV will vary with each individual field and will require additional adjustment including (1) the lateral margins, (2) smearing of compensator (if applicable), (3) range of beam (depth of penetration) and, (4) modulation (number of required Bragg peaks). Adjustments to any of the aforementioned parameters (usually 3-15mm) will be based on the range uncertainty, CT number uncertainty, internal motion, and set up error determined for the particular body site at the individual proton institution. The following parameters must be explicitly reported for each beam: range, modulation, smearing radius of the compensator (if applicable), set-up margin (SM) and PTV margin.

7.3.5.1 Schema I Contouring Volumes:

For patients undergoing mastectomy receiving radiation, the following volumes are to be delineated:

Mastectomy Scar GTV: The mastectomy scar and the surrounding immediate vicinity is a common location for chest wall recurrences post-mastectomy. To ensure this area of the chest wall is adequately covered by post-mastectomy radiotherapy, an initial target volume for the mastectomy scar will be created. The Mastectomy Scar GTV consists of contouring the radio-opaque wire as a surrogate of the scar and con additionally include affected subcutaneous tissue visible on CT per treating physician discretion.

Mastectomy Scar CTV: Mastectomy Scar GTV + 1 cm 3D expansion. Limit the CTV posteriorly at anterior surface of the pectoralis major and anterolaterally at skin and should not cross midline.

Mastectomy Scar PTV: Mastectomy Scar CTV + 7 mm 3D expansion (excludes heart).

Mastectomy Scar PTV Eval: Since a substantial part of the Mastectomy Scar PTV often extends outside the patient a Mastectomy Scar PTV Eval is created. This Mastectomy Scar PTV Eval is limited to exclude the part outside the ipsilateral chest wall and the first 5 mm of tissue under the skin (in order to remove most of the buildup region for the DVH analysis) and posteriorly is limited to exclude lung and heart. The Mastectomy Scar PTV Eval should not cross midline. This is the structure used for DVH constraints and analysis, and not for beam aperture generation.

Chest Wall CTV: Includes the Mastectomy Scar CTV and takes into account the radio-opaque markers placed at CT identifying clinical extent of chest wall, changes visualized by CT, and consensus definitions of anatomical borders of chest wall from the RTOG Breast Atlas, [redacted]

The Chest wall CTV is limited by the skin anteriorly and should not extend deeper than the ribs so that it excludes the lung and heart. Depending on the location of the Mastectomy Scar CTV, it should exclude the sternum medially and the axilla deep to anterior surface of the pectoralis major muscle laterally. In general, the chestwall CTV should not cross midline

Expanders, implants or autologous tissue present for reconstruction will be included in the Chest Wall CTV. The degree of expander expansion present is per the treating physician's discretion. The expander should remain at the same expansion through the course of treatment that is present for the CT simulation.

Chest Wall PTV: Chest Wall CTV +7 mm 3D expansion (exclude heart and do not cross midline).

Chest Wall PTV Eval: As a part of the Chest Wall PTV often extends outside the patient, the Chest Wall PTV is then copied to a Chest Wall PTV Eval, which is edited. This Chest Wall PTV Eval is limited anteriorly to exclude the part outside the patient and the first 5 mm of tissue under the skin (in order to remove most of the buildup region for the DVH analysis) and posteriorly is limited to no deeper than the posterior rib surface and excludes lung and heart. This Chest Wall PTV Eval is the structure used for DVH constraints and analysis and not for beam aperture generation.

7.3.5.2 Schema II Contouring Volumes:

For patients undergoing conservative breast surgery, the following volumes are to be delineated:

Lumpectomy GTV: Contour using all available clinical and radiographic information, including the excision cavity volume, architectural distortion, lumpectomy scar, seroma and/or extent of surgical clips (clips are strongly recommended).

Lumpectomy CTV: Lumpectomy GVT + 1 cm 3D expansion. Limit the CTV posteriorly at anterior surface of the pectoralis major and anterolaterally 5 mm from skin and should not cross midline. In general, the pectoralis and/or serratus anterior muscles are excluded from the lumpectomy CTV unless clinically warranted by the patient's pathology.

Lumpectomy PTV: Lumpectomy CTV + 7 mm 3D expansion (excludes heart).

Lumpectomy PTV Eval: Since a substantial part of the Lumpectomy PTV often extends outside the patient (especially for superficial cavities), the Lumpectomy PTV is then copied to a Lumpectomy PTV Eval, which is edited. This Lumpectomy PTV Eval is limited to exclude the part outside the ipsilateral breast and the first 5mm of tissue under the skin (in order to remove most of the build-up region for the DVH analysis) and excluding the Lumpectomy PTV expansion beyond the posterior extent of breast tissue (chest wall, pectoralis muscles and lung) when pertinent. The lumpectomy PTV should not cross midline. This Lumpectomy PTV Eval is the structure used for DVH constraints and analysis. This Lumpectomy PTV Eval cannot be used for beam aperture generation.

Breast CTV: Includes the palpable breast tissue demarcated with radio-opaque markers at CT simulation, the apparent CT glandular breast tissue visualized by CT, consensus definitions of anatomical borders, and the Lumpectomy CTV from the Breast Cancer Atlas. The breast CTV is limited anteriorly with 5 mm from the skin and posteriorly to the anterior surface of the pectoralis, serratus anterior muscle excluding chest wall, boney thorax and lung. In general, the pectoralis and/or serratus anterior muscles are excluded from the breast CTV unless clinically warranted by the patient's pathology.

The breast CTV should generally follow consensus guidelines [redacted]

Breast PTV: Breast CTV + 5-7 mm 3D expansion (exclude heart and do not cross midline).

Breast PTV Eval: Since a substantial part of the Breast PTV often extends outside the patient, the Breast PTV is then copied to a Breast PTV Eval, which is edited. This Breast PTV Eval is limited anteriorly to exclude the part outside the patient and the first 5 mm of tissue under the skin (in order to remove most of the build-up region for the DVH analysis) and posteriorly is limited to no deeper than the anterior surface of the ribs (excludes boney thorax and lung). This Breast PTV Eval is the structure used for DVH constraints and analysis.

7.3.5.3. Contouring for Regional Nodal Radiation (All Schema I Patients Who Are Receiving Radiation and the Schema II Patients Receiving Regional Nodal Radiation):

Supraclavicular CTV: Based on consensus definitions from the RTOG Breast Cancer Atlas, superior extent typically is below the level of the cricoid; medially excludes thyroid, trachea, esophagus; extends laterally to the edge of the sternocleidomastoid muscle superiorly and the clavicle at its more inferior extent, and the inferior border extends to the caudal aspect of the clavicular head.

Supraclavicular PTV: Supraclavicular CTV + 5mm margin in all directions except medially. The medial border of the Supraclavicular CTV and PTV will be similar. The following structures should be excluded from the Supraclavicular PTV to minimize excess dose to normal tissues: ipsilateral thyroid, trachea, esophagus, and ipsilateral lung. The supraclavicular PTV should exclude the clavicle and vertebral body.

Axillary CTV: The extent of the axilla to be targeted for regional nodal irradiation will depend on which the extent of axillary dissection. See Section 7.3.2.

For patients in Schema I, the axillary CTV consists of the portion of the axilla that remains "undissected". When an axillary node dissection has been done, the inferior border of the axillary CTV will be the most cephalic extent of the dissection. Review of the operative report, postoperative changes on the planning CT, and discussion with the patient's surgeon can be used for determining the most cephalic extent of the dissection and inferior border of the axillary CTV. Axillary dissection typically removes level 1-2 axillary nodes, so that the axillary CTV in these cases is expected to include level 3 primarily and some of level 2 of the axilla. If the level I axilla alone is dissected, then levels II-III of the axilla should be included in the Axillary CTV. If the level I-II axilla are dissected, the level III of the axilla should be targeted and some of the level II may be included. If the level I-III axilla are dissected, then there will be no Axillary CTV unless there is a very high nodal burden of disease. The lateral and inferior border of the CTV is, therefore left at some discretion to the radiation oncologist.

If a sentinel lymph node biopsy alone is performed and patients are indicated for regional nodal radiation as outlined in Section 7.3.1, then the Axillary CTV includes all of Level I, II and III nodes as defined in the RTOG Breast Atlas. Any clips left from the sentinel node procedure should be included in the CTV and treatment field.

Axillary PTV: Axillary CTV + 5 mm except the medial border. The medial border of the Axillary PTV will be similar to the Axillary CTV. The ipsilateral lung should be excluded from the Axillary PTV.

Internal Mammary Node (IMN) CTV: Includes the internal mammary/thoracic vessels in the first three intercostal spaces.

Internal Mammary Node (IMN) PTV: The IMN CTV + 5 mm expansion, medially and laterally. The IMN PTV is limited medially to not extend beyond the lateral aspect of the sternum. In order to minimize the excess normal tissue irradiation, no additional expansion into the lung should be done for the IMN PTV. The deep edge of the IMN PTV will be similar to the IMN CTV. No anterior expansion into the chest wall or breast volumes will be done.

The following naming convention is to be used in the treatment planning system:

Structure List for Right Breast Cancer

Description	Planning System Name
Lumpectomy GTV	GTV_Lump_R
Lumpectomy CTV	CTV_Lump_R
Lumpectomy PTV	PTV_Lump_R
Lumpectomy PTV_Eval	PTV_Lump_Eval_R
Mastectomy Scar GTV	GTV_Scar_R
Mastectomy Scar CTV	CTV_Scar_R
Chest Wall CTV	CTV_CW_R
Chest Wall PTV	PTV_CW_R
Chest Wall PTV_Eval	PTV_CW_Eval_R
Supraclavicular CTV	CTVn_SCL_R
Supraclavicular PTV	PTVn_SCL_R
Axillary CTV	CTVn_Ax_R
Axillary PTV	PTVn_AX_R
Internal Mammary Node CTV	CTVn_IMN_R
Internal Mammary Node PTV	PTVn_IMN_R
Ipsilateral Lung	Lung_R
Contralateral Lung	Lung_L
Heart	Heart
Contralateral Breast or Chest Wall	Breast_L
Thyroid	Thyroid

Structure List for Left Breast Cancer

Description	Planning System Name
Lumpectomy GTV	GTV_Lump_L
Lumpectomy CTV	CTV_Lump_L
Lumpectomy PTV	PTV_Lump_L
Lumpectomy PTV_Eval	PTV_Lump_Eval_L
Mastectomy Scar GTV	GTV_Scar_L
Mastectomy Scar CTV	CTV_Scar_L
Chest Wall CTV	CTV_CW_L
Chest Wall PTV	PTV_CW_L
Chest Wall PTV_Eval	PTV_CW_Eval_L

Supraclavicular CTV	CTVn_SCL_L
Supraclavicular PTV	PTVn_SCL_L
Axillary CTV	CTVn_Ax_L
Axillary PTV	PTVn_IMN_AX_L
Internal Mammary Node CTV	CTVn_IMN_L
Internal Mammary Node PTV	PTVn_IMN_L
Ipsilateral Lung	Lung_L
Contralateral Lung	Lung_R
Heart	Heart
Contralateral Breast or Chest Wall	Breast_R
Thyroid	Thyroid

Dose Volume Histogram (DVH) Analysis is Required

Chestwall or Breast (For Schema I or II):

Per Protocol: ≥ 95% of the Chestwall or Breast PTV Eval will receive 95% of the prescribed dose.

Variation Acceptable: ≥ 90% of the Chestwall or Breast PTV Eval will receive ≥ 90% of the prescribed dose.

Maximum Dose to Chestwall or Breast PTV_Eval (calculated without the inclusion of the boost.

Per protocol:

Photon and proton only plans:

< 10cc of Chestwall or Breast PTV Eval will receive ≥ 107% of the prescribed dose (up to 110% allowed).

<0.03cc Chestwall or Breast PTV Eval can receive >115% of the prescribed dose (up to 120% allowed).

Composite photon/electron plans:

<10cc of Chestwall or Breast PTV Eval will receive ≥ 110% of the prescribed dose (up to 115% allowed).

<0.03cc Chestwall or Breast PTV Eval can receive 120% of the prescribed dose (up to 130% allowed).

Lumpectomy Boost PTV Eval (calculated only if boost used) (For Schema II):

Per Protocol: ≥ 95% of the Lumpectomy PTV Eval receives ≥ 95% of the prescribed dose.

Variation Acceptable: ≥ 90% of the Lumpectomy PTV Eval will receive ≥ 90% of the prescribed dose.

Per Protocol: < 10cc of the Lumpectomy PTV Eval receives 110% of the prescribed dose.

Per protocol: <0.03cc of the Lumpectomy PTV Eval receives 120% of the prescribed dose.

Supraclavicular (SCL) PTV:

Per Protocol: ≥ 95% of the SCL PTV will receive ≥ 95% of the prescribed dose

Variation Acceptable: ≥ 90% of the Supraclavicular PTV will receive ≥ 90% of the prescribed dose

Maximum dose to SCL PTV: <0.03cc can receive greater than 110% of the prescribed dose.

Axillary PTV:

Per Protocol: ≥ 95% of the Axillary PTV will receive ≥ 95% of the prescribed dose

Variation Acceptable: ≥ 90% of the Axillary PTV will receive ≥ 90% of the prescribed dose

Maximum dose to Axillary PTV: <0.03cc can receive greater than 110% of the prescribed dose.

Internal mammary nodal (IMN) PTV:

Per Protocol: ≥ 90% of the IMN PTV will receive ≥ 90% of the prescribed dose

Variation Acceptable: ≥ 90% of the IMN PTV Eval will receive ≥ 80% of the prescribed dose

Contralateral Breast:

Per Protocol: Less than 10% of the contralateral breast receives ≥ 3 Gy

Variation Acceptable: Less than 10% of the contralateral breast receives ≥ 5Gy

Ipsilateral Lung:

Schema I and Schema II Receiving Regional Nodal Radiation:

Per Protocol: ≤ 35% of the ipsilateral lung should receive ≥ 20 Gy for standard fractionation and ≥ 18 Gy for hypofractionation

Variation Acceptable: ≤ 40 % of the ipsilateral lung should receive ≥ 20 Gy for standard fractionation and ≥ 18 Gy for hypofractionation

Schema II Not Receiving Regional Nodal Radiation:

Per Protocol: ≤ 15% of the ipsilateral lung should receive ≥ 20 Gy for standard fractionation and ≥ 18 Gy for hypofractionation

Variation Acceptable: ≤ % 17 of the ipsilateral lung should receive ≥ 20 Gy for standard fractionation and ≥ 18 Gy for hypofractionation

Contralateral Lung:

Schema I and Schema II:

Per Protocol: ≤ 10% of the contralateral lung should receive ≥ 5 Gy

Variation Acceptable is ≤ 15% of the contralateral lung should receive ≥ 5 Gy

Heart:

Left Sided Cancer:

Per protocol: Mean heart dose ≤ 3 Gy and ≤ 10% heart receives 25 Gy

Variation Acceptable: Mean heart dose ≤ 5 Gy and ≤ 10% heart receives 30 Gy

Right Sided Cancer:

Per protocol: Mean heart dose ≤ 2 Gy or ≤ 2% heart receives 25 Gy

Variation Acceptable: Mean heart dose ≤ 5 Gy or ≤ 2% heart receives 30 Gy

**Every attempt should be made to make the cardiac exposure to radiation as low as possible.

7.4 Radiation Therapy Quality Assurance

Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan and dose files. This study uses TRIAD for RT data submission. Use of TRIAD requires several preliminary steps.

Additional information is available at:

[redacted]

In the event that a site has not completed all steps required for TRIAD data submission in time to meet the timeline for review, data submitted via SFTP will also be accepted. See instructions for submission of data via SFTP on the IROC Rhode Island website under Digital Data [redacted]).

All required data should be submitted within one week of the completion of radiotherapy, as outlined in Section 7.4.4. In the event that a site submits plans for two or more cases requiring major revisions or having unacceptable deviations, the site may be asked to submit plans prior to treatment for subsequent patients.

7.4.1 Definitions of deviations in protocol performance

Per Protocol: All specified DVH requirements identified as "Preferred" have been met.

Variation Acceptable: Specified DVH requirements within the "Acceptable" range have been met.

Deviation Unacceptable: Specified DVH requirements for Variation Acceptable are not met.

7.4.2 Definitions of deviations in volumes drawn

Per protocol: All specified contouring volumes are drawn as specified in the protocol.

Variation Acceptable: Delineation of specified contouring volumes deviates from protocol guidelines, but the protocol intended volumes are adequately covered by the prescribed doses.

Deviation Unacceptable: Delineation of specified contouring volumes deviates significantly from protocol guidelines and the protocol intended volumes are not adequately covered by the prescribed doses.

7.4.3 Dose modifications and management of toxicity

Radiation doses should not be modified and compliance with the protocol will be determined as defined above, by the ideal and acceptable dose constraint criteria. Dose deviations outside of the acceptable range will be considered major protocol deviations. Patients may occasionally require treatment breaks, which should be kept to a minimum. Treatment breaks of up to 1 calendar week will be considered acceptable. Treatment breaks

of greater than 1 week are considered deviations. Patients with deviations should continue treatment per protocol and will be included in the study analysis, as this is an intention to treat analysis.

7.4.4 Quality Assurance Documentation

Digital Submission:

Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan and dose files. Data Submission via TRIAD is preferred. See Section 6.2 for TRIAD Requirements. Alternative instructions for data submission are on the IROC Rhode Island Web site at [redacted] Any items on the list below that are not part of the digital submission may be submitted as screen captures along with the digital data.

Submission of data is required on all patients receiving radiation. It should be noted that radiation therapy does not require pre-approval to initiate treatment. The following data will be submitted:

Treatment Planning System Output

- RT treatment plan including CT, structures, dose, and plan files. These items are included in the digital plan.
- DRR's are not required for IMRT.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

Supportive Data and Forms

- Copies of operative & pathology reports for all of the following applicable procedures: lumpectomy/mastectomy/SLN/ALND/re-excision/ARM.
- RT-1 or Proton Dosimetry Summary Form
- The RT-2 Radiotherapy Total Dose Record form.
- A copy of the patient's radiotherapy record including prescription, and the daily and cumulative doses to all required areas, critical organ and reference points

Supportive Data and Forms may be included with the transmission of the digital RT data via sFTP or submitted separately via e-mail to [redacted]

Questions regarding the dose calculations or documentation should be directed to:

[redacted]

7.5 External Facilities

Radiation therapy per Sections 7.3 and 7.4 may be performed at external radiation therapy facilities, if the following additional requirement is met:

- Approval by Imaging and Radiation Oncology Core (IROC) according to Section 14.1, Institutional Credentialing.

8.0 DOSE AND TREATMENT MODIFICATIONS, UNBLINDING

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

As a general rule, simultaneous enrollment on any other treatment study, with or without investigational agents, is discouraged, although exceptions may be allowed in unusual circumstances by the study chair in collaboration with the executive officer and primary statistician.

Co-enrollment is allowed and encouraged on the following trials, if patients meet eligibility criteria for those trials: A221505 and MA.39. For patients who co-enroll on those trials, please follow the dose constraints on the corresponding trial.

8.1.1 Patients should not receive any other treatment which would be considered treatment for the primary neoplasm or impact the primary endpoint.

This includes any surgical intervention other than that described by the protocol, radiotherapy, cryotherapy, ablation, etc., performed on the primary neoplasm.

8.1.2 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 Treatment with hormones or other chemotherapeutic agents may be administered, including steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic in solid tumor protocols. Use of dexamethasone and other steroidal antiemetics is prohibited in leukemia and lymphoma protocols.

8.1.4 Antiemetics may be used at the discretion of the attending physician, with the exception of steroids above.

8.1.5 Hypersensitivity/infusion reactions

Treat hypersensitivity and infusion reactions to Lymphazurin as per institutional standards.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at [redacted] Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the Form, "Adverse Events" is used for routine AE reporting in Rave.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v5.0 Term	CTCAE v5.0 System Organ Class (SOC)
• Lymphedema	• Vascular disorders

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting.

The CTCAE is identified and located on the CTEP website at: [redacted] All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE ≤ 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>• Grade 1 Timeframes</th><th>• Grade 2 Timeframes</th><th>• Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour;
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

9.3.2 Expedited AE reporting timelines defined

"24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.

"10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

9.3.3 Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

Grade 3/4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.

Reporting of cases of secondary AML/MDS is to be done using the NCI/CTEP Secondary AML/MDS Report Form. New primary malignancies should be reported using study Form Notice of New Primary.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE version 5.0, the new malignancies (both second and secondary) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic

syndrome, (3) Treatment-related secondary malignancy, or (4) Neoplasms benign, malignant and unspecified-other. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and submitted, along with any additional medical information (form is available on the CTEP website at [redacted]). The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

Pregnancy loss

• Pregnancy loss is defined in CTCAE as "Death in utero."

• Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.

• A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEPAERS recognizes this event as a patient death.

10.0 DRUG INFORMATION

10.1 General Considerations:

All study agents are to be administered at the registering institution.

10.2 Isosulfan Blue Dye (Lymphazurin®)

Isosulfan Blue is a synthetic visual lymphatic imaging agent. Isosulfan blue upon subcutaneous administration, delineates the lymphatic vessels draining the region of injection. It is an adjunct to lymphography in: primary and secondary lymphedema of the extremities; chyluria, chylous ascites or chylothorax; lymph node involvement by primary or secondary neoplasm; lymph node response to therapeutic modalities.

IND Exempt: Isosulfan Blue Dye is IND exempt as used in this trial. This exemption has been determined by attestation that neither the investigator nor sponsor intends to seek a new indication for use or to support any other significant change in the labeling or product advertising for Lymphazurin; this investigation will use an approved route of administration and dosage of Lymphazurin and has no factors that increase the risk of the product; this investigation will be in compliance with 21CFR parts 56, 50, and 312.7; and neither the investigator nor sponsor will promote or represent that Lymphazurin is safe or effective for the context that is under investigation in this study.

Procurement

Pharmacies or clinics shall obtain supplies from normal commercial supply chain or Wholesaler.
Formulation

Isosulfan Blue injection 1% is supplied as a 50 mg/5 mL (10 mg/mL) single-dose vial. It is a 1% aqueous solution in a phosphate buffer prepared by appropriate manufacturing to be sterile and pyrogen-free. Each mL contains isosulfan blue 10 mg, Sodium monohydrogen phosphate 6.6 mg, Potassium dihydrogen phosphate 2.7 mg.

Preparation, storage and stability

Do not mix isosulfan blue with local anesthetics as this results in an immediate precipitation. Use a separate syringe to administer a local anesthetic. Vials should be stored at 20˚C to 25˚C (68˚ to 77˚F). Avoid excessive heat.

Administration

Isosulfan blue injection 1% is to be administered subcutaneously, in upper inner volar surface of the index extremity per study. A maximum dose of 5 mL is to be injected.

Drug Interactions

No drug interactions have been identified with isosulfan blue injection 1%

Pharmacokinetics

Excretion: Up to 10% of the subcutaneously administered dose of isosulfan blue injection 1% is excreted unchanged in the urine in 24 hours in humans.

Adverse Events

Hypersensitivity reactions (respiratory distress, shock, angioedema). Reactions are more likely to occur in patients with a history or bronchial asthma, allergies, drug reactions or previous reaction to triphenylmethane dyes. Interference with oxygen saturation and methemoglobin measurements. Transient or long-term (tattooing) blue coloration.

11.0 MEASUREMENT OF EFFECT

11.1 Measurement of Lymphedema:

Patients will undergo a total of four lymphedema assessments at the following time periods of both upper extremities (UE): Pre-surgery/baseline and then annually at 12, 24 and up to 36 months at their regularly scheduled follow-up visits. This time period is chosen because the onset of lymphedema varies, with two-thirds becoming evident within 2 years of surgery and 97% within 3 years of surgery. (55) Body mass index (BMI) and bilateral UE circumference measurements will be collected.

Total limb volume can be measured by water displacement (51), conic geometry (52), perometry (53), or tissue changes by tonometry (54). This study will use conical geometric LE assessment (52). A patient will be considered to have developed UE lymphedema if there is a 10% increase in the volume of her ipsilateral UE from its pre-surgery volume. Circumferential measurement of limb volume will be performed on both affected and non-affected UEs. Patients will sit with their UEs resting horizontally palms-down on a bedside table placed at a level slightly below the axilla. The patients will be instructed to wear loose sleeves or short sleeves and to remove any jewelry prior to the measurement. Measurements will be taken, as was done in CALGB 70305 and Alliance A221505, at the wrist, half way between the wrist and antecubital fossa (below the elbow), at the antecubital fossa, half way between the antecubital fossa and the axilla, and at the axilla. In all cases, the plane of the tape around the UE will be held perpendicular to the long axis of the UE and perpendicular to the floor. The tape will be held snugly around the body part without indenting the skin or compressing subcutaneous adipose tissue. If gaps between the skin and tape are seen in some individuals, tension should not be increased to reduce the gap. Measurements of the UE and other required data will be recorded on the Body Diagram case report form. The standard formula (based on cylindrical slices) will be utilized in this study to calculate volume (V) from circumference (U) measures.

The patient will also be given a grade, from 1-3, of their lymphedema according to CTCAE (version 5.0). The grade will also be used to quantify the severity/degree of LE between arms which is an important outcome for the patient and in general has not been reported in a majority of clinical trials.

11.2 Technical Success of ARM Procedure

Technical success is injecting correct sites as designated per the protocol. Identification and sparing of blue dye in axillary node.

A cross over node is defined as a blue node that has counts 10 percent over the background of the axilla.

11.3 Recurrence

11.3.1 Local recurrence

Local recurrence is defined as histologic evidence of ductal carcinoma in situ or invasive breast cancer in the ipsilateral beast or chest wall.

11.3.2 Regional recurrence

Regional recurrence is defined as the cytologic or histologic evidence of disease in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular and/or ipsilateral axillary nodes or soft tissue of the ipsilateral axilla.

11.3.3 Distant recurrence

Distant recurrence is defined as the cytologic, histologic and/or radiographic evidence of disease in the skin, subcutaneous tissue, lymph nodes (other than local or regional metastasis), lung, bone marrow, central nervous system or histologic and/or radiographic evidence of skeletal or liver metastasis.

11.4 Patient reported outcomes:

The aim of the health-related quality of life (HRQoL) endpoints is to provide a better understanding of patients' experience related to their HRQoL between the treatment arms. These endpoints provide a holistic context to interpret the results of the primary endpoint. The following questionnaire will be completed at baseline visits, then annually at 12, 24, and up to 36 months.

11.4.1 Lymphedema Symptom Intensity and Distress Survey- Arm (LSIDS-A)

We will use the Lymphedema Symptom Intensity and Distress Survey-Arm (LSIDS-A) which is a 30-item scale that has been validated as a reliable instrument to assess arm lymphedema and its associated symptoms.[57] It should take patients approximately 10-15 minutes to complete this survey.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Protocol Treatment

For the purpose of this study, protocol treatment is defined as the surgical intervention. Patients who complete surgery and any adjuvant therapy as described in Section 7.0 will be followed as outlined in Section 5.0 for 3 years after the completion of surgery.

12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- If patient becomes pregnant prior to surgery.
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Termination of the study by sponsor

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

12.3 Follow-up

Patients who complete surgery and any adjuvant therapy as described in Section 7.0 will be followed as outlined in Section 5.0 for 3 years after the completion of surgery.

No further follow up will be required for patients who withdraw from the lymphedema assessments. Submission of questionnaires and patient-reported outcomes for these patients is encouraged but will not be required.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

12.5 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline and off treatment notice data submission is required. See the Data Submission Schedule accompanying the All Forms Packet.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Overview:

This trial is designed as a multi-center, randomized phase III trial to study the rate of lymphedema after sentinel lymph node biopsy and sentinel lymph node biopsy followed by axillary lymph node dissection where patients will be randomly assigned at a ratio of 1:1 to receive either axillary reverse mapping (ARM) or no ARM.

13.2 Sample Size, Accrual time and Study duration

13.2.1 Sample size

The primary endpoint of this trial is the incidence of UE lymphedema within 36 months of SLNB +/- ALND. Assume that, among individuals not receiving ARM, 7% of patients receiving SLNB without ALND and 20% of SLN positive patients receiving ALND will

experience UE lymphedema within 36 months (19-24) and that among individuals receiving ARM, 2.5% of patients receiving SLNB without ALND and 6% of SLN positive patients receiving ALND will experience UE lymphedema within 36 months. We expect that 30% of the patients enrolled in this study will have clinically positive nodes at trial registration and will go on to have ALND. The other 70% of patients enrolled will have clinically negative nodes at trial registration. It is expected that one third (1/3) of the patients with clinically negative nodes at trial registration will end up having positive SLNB. Among these patients, 70% will go on to have ALND. All other patients will not receive ALND. In summary, we expect 46% (= 0.3 + 0.7*0.7/3)) of patients will receive ALND and 54% will not receive ALND. Thus, the expected overall proportions of patients experiencing UE lymphedema within 36 months is 13% [= (0.54 x 0.07) + (0.46 x 0.20)] in Group I (no ARM) and 4.12% [= (0.54 x 0.025) + (0.46 x 0.06)] in Group II (ARM). Estimates are based on a compilation of studies for SLN only (Table I) and a large Phase II trial for ARM. (45) To further account for a 10% mortality prior to diagnosis of lymphedema, the study is designed to compare the cumulative incidence of UE lymphedema treating death as the competing risk assuming the cumulative incidence of UE lymphedema is 11.7% vs. 3.7% for the Group I and Group II, respectively.

Using a 1:1 randomization, a sample size of 464 patients (232 per arm) will provide 90% power at a two-sided type I error of 5% to detect a reduction in 36-month cumulative incidence of lymphedema from 11.7% in Group I (no ARM) to 3.7% in Group II (ARM) with one planned interim analysis for futility and efficacy after 50% of evaluable patients have been followed for the primary endpoint of 36-month lymphedema. The efficacy and futility (non-binding) boundaries were determined using the Lan-DeMets spending functions. Assuming assessment 10% drop-out due to cancellations or protocol violation, the target accrual will be inflated by 10% to a total of 516 (258/group) patients.

This sample size also provides sufficient power to detect clinically meaningful effect of treatment on HRQoL secondary endpoints. If the primary endpoint results indicate a reduction in lymphedema with the ARM treatment, analyses will be conducted to compare the LSIDS-A scores between the treatment groups. To adjust for the family type I error, each of these endpoints will be compared using a two-sided error rate of 0.025. A total of 396 evaluable patients will provide 84% power to detect a change in HRQoL scores of .3 standard deviations (effect size) which is a moderate effect size which we consider a clinically meaningful change for these HRQoL instruments. All sample size calculations were performed using EAST v6.4.

13.2.2 Accrual rate and accrual duration

Assuming an accrual rate of approximately 20 patients per month, the anticipated accrual period is 26 months with completion of primary aim by 62 months.

13.3 Statement of Primary Endpoint

13.3.1 Primary Endpoint

The primary endpoint is comparison of the cumulative incidence of UE lymphedema at 36-months post-surgery between the two study groups (ARM versus no-ARM). A patient will be considered to have developed UE lymphedema if there is a 10% increase in the volume of her ipsilateral UE from its pre-surgery volume after adjusting for percent change in BMI. Physician diagnosed lymphedema will still need to be confirmed by arm circumference measurements.

13.3.2 Statistical Design

Interim analysis decision rule:

Interim analysis for efficacy and futility (non-binding) will be conducted when 50% of evaluable patients have reached the primary endpoint of 36-month lymphedema. The Lan-DeMets family of alpha and beta spending functions corresponding to the O'Brien-Fleming boundary are used for controlling overall type I and type II error rates. The trial will be terminated for efficacy if the 2-sided p-value at the interim analysis is < 0.003 with a conclusion of ARM superiority if the Z score (LE incidence after ARM minus LE incidence after no-ARM) is < -2.963 and conclusion of ARM inferiority if $Z > 2.963$. The trial will be terminated for futility of the ARM treatment $p > 0.844$ (corresponding to $-0.196 < Z < 0.196$. The second stage of this clinical trial shall continue if p-value is in the interval of (0.003, 0.844).

Final analysis decision rule:

The final analysis will be conducted when all patients have been enrolled and evaluable for the primary endpoint. Superiority of ARM will be concluded if p-value ≤ 0.049 (corresponding to $Z < -1.969$) and futility of ARM will be concluded if p-value > 0.049 (corresponding to $Z >= 1.969$).

13.3.3 Study Operating Characteristics

Simulation studies of 10,000 clinical trials are conducted for the proposed group sequential design. The probabilities of early stopping (at the interim analysis) and empirical powers for various scenarios are summarized in the following table. Of particular interest, assuming that the 36-month cumulative incidence of UE lymphedema in the no-ARM group is 11.7 % and the 36-month cumulative incidence of UE lymphedema in the ARM group is 11.7% (that is, ARM has no effect on lymphedema at 36 months post treatment), there is a 15% chance that the trial will stop at the interim analysis with the conclusion that ARM has no effect on lymphedema and there is a total of 5% chance of the trial will conclude that the 36-month UE lymphedema incidences differ between the treatment groups (type I error). In another scenario where the 36-month cumulative incidence of UE lymphedema in the no-ARM group is 11.7 % and the 36-month cumulative incidence of UE lymphedema in the ARM group is 3.7% (that is, ARM reduces incidence of lymphedema at 36 months post treatment), there is a 21% chance that the trial will stop at the interim analysis with the conclusion that the lymphedema rates differ between the treatment groups and there is a total of 91% chance of the trial will conclude that the 36-month UE lymphedema incidence differ between the treatment groups (power).

Incidence of LE 36-months post treatment		Interim analysis conclusion		Early stopping	Final analysis conclusion		Power
No-ARM	ARM	Efficacy	Futility		Efficacy	Futility	
11.7%	11.7%	0.35%	14.59%	14.94%	4.75%	80.31%	5.10%
	8%	1.66%	6.46%	8.12%	23.98%	67.9%	25.64%
	6%	5.95%	2.95%	8.90%	51.51%	39.59%	57.46%
	3.7%	21.14%	0.60%	21.74%	69.53%	8.73%	90.67%

13.3.4 Analysis Plan for Primary Endpoint

The cumulative incidence of lymphedema at 12, 24, and 36 months post-surgery will be estimated by treatment group using the cumulative incidence function treating death as a

competing risk. The event for this endpoint is a diagnosis of lymphedema. The time interval for this endpoint is the time interval from study entry to lymphedema diagnosis, death, or last follow-up whichever occurs first. Without censoring, this estimate is equivalent to the simple proportion of patients who are diagnosed with lymphedema within the first 12, 24, and 36 months post-surgery out of all patients randomized to that treatment group. The cumulative incidence of lymphedema at 36-months post-surgery will be compared between the two study groups (ARM vs no ARM) using a two-sample test of proportions (i.e. a Z-test using a normal approximation), at a two-sided 5% significance level.

In an additional analysis a pseudo-value approach by Andersen and Klein will be implemented to compare the cumulative incidence of UE lymphedema to adjust for the stratification factors. (59)

13.4 Secondary endpoints Analysis Plans

13.4.1 Secondary Endpoints

13.4.1.1 Comparison of change in health-related quality of life from baseline to 36 months, as measured by the LSIDS-A.

13.4.1.2 Comparison of the incidence of regional recurrence between study groups.

13.4.1.3 Estimation of the rate of technical success of performance of ARM procedure (defined as identification of ARM lymphatics, and the ability to spare or reapproximate ARM lymphatics) between study groups.

13.4.2 Secondary Endpoints Analysis

13.4.2.1 The LSIDS-A will be derived based on its established algorithm. The LSIDS-A questionnaire scores for swelling in the arm, decreased physical activity, pain in the arm, and loss of confidence in one's body will be evaluated for the change of baseline to 36 months using a two-sample, two-sided t-test. All other analyses will be exploratory and hypothesis generating, including: graphical procedures will include stream plots of individual patient scores and plots of average values over time for each study group. The LSIDS-A questionnaire scores at each time point, as well as the change from baseline will be compared between groups by a two-sample, two-sided t-test. If there is evidence of non-normality (via Shapiro-Wilk testing), we'll use a non-parametric procedure such as Wilcoxon rank sum test. Further analysis will include linear mixed model using data from all time points to compare the LSIDS-A questionnaire scores between the two treatment groups over time adjusting for other baseline characteristics. We will evaluate the pattern of missing data. If the drop-out rate is higher than expected, methods proposed by Hogan and Laird (58) will be used to assess whether the presence of drop-outs affects inferences obtained from the repeated measures analyses. Appropriate methods will be used to address missingness.

13.4.2.2 The technical success will be summarized using a binomial point estimate and 95% confidence interval (CI).

13.4.2.3 The cumulative incidence of regional recurrence will be summarized using the cumulative incidence function treating death without regional recurrence as the competing risk. Similar analysis methods described for the primary endpoint will be used to compare the cumulative incidence of regional recurrence between group I and II.

13.5 Exploratory endpoint:

The effect of the use of radiotherapy (Yes vs. no) and of lymph node basins on Lymphedema (LE) rate measure at 12, 24, and 36 months will be explored using the repeated measure pseudo-value approach, using the generalized estimating equation, adjusted for treatment groups and other baseline characteristics that might be associated with LE.

13.6 Study Monitoring

13.6.1 Data Safety Monitoring

This study will be monitored by the Alliance Data Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines.

13.6.2 Interim Analysis

Interim analysis for efficacy and futility (non-binding) will be conducted when 50% of evaluable patients have reached the primary endpoint of 36-month lymphedema. The Lan-DeMets family of alpha and beta spending functions corresponding to the O'Brien-Fleming boundary are used for controlling overall type I and type II error rates. The trial will be terminated for efficacy if the 2-sided p-value at the interim analysis is < 0.003 with a conclusion of ARM superiority if the Z score (LE incidence after ARM minus LE incidence after no-ARM) is $< -2.958\,963$ and conclusion of ARM inferiority if $Z > 2.958963$. The trial will be terminated for futility of the ARM treatment $p > 0.838\,844$ (corresponding to $-0.204\,196 < Z < 0.204196$. The second stage of this clinical trial shall continue if p-value is in the interval of (0.003, 0.838844).

13.6.3 Accrual Monitoring Stopping Rule

Patient accrual will be closely monitored by the investigators and study statistician on a bi-weekly basis. If the accrual rate falls below 50% of expected accrual rate, investigators will carefully review feedback from sites and consider taking measures to encourage patient enrollment.

13.7 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race or ethnic origin.

We are not aware of any evidence suggesting differential effects of axillary reverse mapping on lymphedema by race or ethnicity, and do not believe such differential effects are likely to exist. As part of our analysis, we will assess the degree to which treatment effects vary across race and ethnicity to ensure that the above assumption is reasonable. It should be noted that this study is powered for the primary analysis, and thus such subgroup analyses were not taken into account when estimating our target sample size.

The geographical region served by the Alliance has a population which includes approximately 13.5% minorities. However, we will work with the Alliance NCORP Health Disparities Committee to enrich minority enrollment to this trial and expect 21% of patients enrolled to this trial to be classified as minorities. Expected sizes of race by ethnicity subsets for patients randomized to this study are shown in the following table.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	2	0	0	0	2
Asian	12	0	1	0	13
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	51	0	2	0	53
White	408	0	24	0	432
More Than One Race	7	0	8	0	15
Total	481	0	35	0	516

14.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING

14.1 Institutional Credentialing

14.1.1 IROC Institutional Requirements

Either 3D conformal or Intensity Modulated Radiation Therapy (IMRT) planning techniques are allowed on this study. Proton therapy is allowed for sites that have met the the baseline approval and credentialing requirements for its use.

Institutions using IMRT or Protons must be credentialed prior to delivery of radiation therapy on any protocol patient. Institutions previously credentialed for use of IMRT in clinical trials need not repeat IMRT credentialing for this trial.

Allowable proton modes of delivery include scattering, uniform scanning and pencil beam scanning provided that the delivery mode has been specifically credentialed by the IROC Houston QA Center. Investigators using protons must comply with current NCI proton therapy guidelines as outlined in the Guidelines for the Use of Proton Radiation Therapy in NCI Sponsored Cooperative Group Clinical Trials, available at [redacted]

Web Link for Credentialing Procedures and Instructions: [redacted]

	Treatment Modality		
RT Credentialing Requirements	**IMRT**	**PROTON**	**Key Information**
Facility Questionnaire	**X**	**X**	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email [redacted] to receive your FQ link.
Credentialing Status Inquiry form	**X**	**X**	To determine if your institution has completed the credentialing requirements, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website [redacted]
Phantom Irradiation	**X**	**X**	Sites treating with IMRT and not previously credentialed for its use must irradiate IROC Houston's IMRT head and neck phantom. Proton centers must complete all required phantom irradiations for IROC Houston baseline approval. Instructions for requesting and irradiating the phantoms are found on the IROC Houston web site. [redacted]
			Institutions will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center

Institution				will notify the institution and Alliance Headquarters that all desired credentialing requirements have been met.

14.2 Individual Credentialing

14.2.1 Surgical Credentialing

A training seminar will be held prior to activation of the study and will be repeated at Alliance meetings semi-annually, as necessary. However, surgeons are not required to attend training sessions in person. Participating surgeons will be required to watch a training video that details how to inject the dye, which is posted on the Alliance and CTSU websites at: [redacted]

The video demonstrates the various anatomical variations that can be encountered. A surgeon interested in participating in this trial will then be required to perform and submit case reports for at least 2 cases (done on patients who are not on this clinical trial) to be reviewed by a member of the study team. The three members of the study team who will approve the training are [redacted] (see protocol cover page for emails). Please submit your case reports (along with de-identified operative notes) to one of these individuals. If properly performed and submitted, the surgeon will be allowed to accrue to the study. If not, additional cases will need to be performed and case reports reviewed by the study surgical chairs until ARM is judged to be properly performed by the individual surgeon.

Case reports for patients entered on this trial will need also to be submitted for each investigator. They will be reviewed to assure that proper techniques are being used. As necessary, the co-Chairs and Community Co-Lead, who are all proficient in this technique, are available via phone (see protocol cover page for phone information) as well as on-site to preceptor investigating surgeons, as necessary.

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16.0 MODEL CONSENT FORM

Study Title for Participants: A Trial of Axillary Reverse Mapping Added to Usual Axillary Surgery to Prevent Lymphedema after Surgery for Breast Cancer

Official Study Title for Internet Search on [redacted]: Alliance A221702, ARM: Axillary Reverse Mapping- A Prospective Trial to Study Rates of Lymphedema and Regional Recurrence after Sentinel Lymph Node Biopsy and Sentinel Lymph Node Biopsy Followed by Axillary Lymph Node Dissection With and Without Axillary Reverse Mapping
(NCT03927027)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have invasive breast cancer that requires staging of your lymph nodes in your armpit area. Staging is a procedure used to evaluate how far your cancer has spread.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

This study is conducted by the Alliance for Clinical Trials in Oncology, a national clinical research group supported by the National Cancer Institute. The Alliance is made up of cancer doctors, health professionals, and laboratory researchers, whose goal is to develop better

treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of cancer patients.

Why is this study being done?

This study is being done to answer the following question:

Can we lower your chance of developing lymphedema (swelling of your arm) by looking at how your lymph node system drains into your arm so these drainage paths can be protected during surgery?

We are doing this study because we want to find out if an added procedure during your breast cancer surgery is better than the usual approach for reducing the chance of developing swelling in the arm. The usual approach is defined as care most people get for breast cancer.

What is the usual approach to my breast cancer?

The usual surgical approach for invasive breast cancer is either a lumpectomy or a mastectomy and staging of the lymph nodes. A lumpectomy is removal of the tumor and a tumor free zone around the tumor. Mastectomy is removal of all of your breast. Staging is sampling of the nodes under your arm to determine if cancer has spread to them. Usually, staging of the lymph nodes is done by a sentinel lymph node biopsy. A sentinel node is the first lymph node to which cancer cells are most likely to spread from a primary tumor in your breast. The surgeon injects a tracer in the breast that will follow the same route as potential tumor cells to the sentinel lymph node. Injecting a dye or tracer will indicate to which node under the arm the tumor is draining. If the nodes do not contain cancer that is all of the staging that is needed. If the nodes do contain cancer, further staging by an axillary lymph node dissection (removal) may be necessary. When lymph nodes are removed, patients are at higher risk for developing lymphedema (swelling of the arms).

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.

What will happen if I decide to take part in this study?

If you decide to take part in this study, in addition to the sentinel lymph node and/or axillary lymph node dissection, you will either get blue dye injected into your upper extremity to locate the lymph nodes draining from your upper extremity during surgery (this is called axillary reverse mapping or ARM), or you will not.

Additionally, we will measure both of your arms to determine if there is any swelling at four different times, before your surgery and at your 12, 24 and 36-month follow-up visits. This will be done by measuring your arm with a tape measure starting at the wrist, the elbow and halfway in-between, then the arm at the level of the armpit and halfway in-between the elbow and the armpit. Both arms will be measured. You will also fill out one questionnaire before your surgery and at your 12, 24 and 36-month follow-up visits. The questionnaire may take up to 15 minutes to complete.

After you finish your surgical treatment, your doctor and study team will watch you for side effects of surgery including lymphedema and other upper arm problems one month after surgery and at your usual 12, 24 and 36-month follow-up visits.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is the risk that adding axillary reverse mapping to your axillary staging procedure may not be any better than the usual axillary staging procedure alone.

There is also a risk that you could have side effects from the blue dye used in axillary staging. These side effects may be worse and may be different than you would get with the usual approach for your staging.

Some of the most common side effects that the study doctors know about are:

- Allergy to the blue dye. In rare cases, this could be life threatening.
- Staining of skin from blue dye
- Discoloration of urine up to 24 hours after injection

There may be some risks that the study doctors do not yet know about.

Benefits

There is evidence that this axillary reverse mapping is effective in preventing arm swelling after breast cancer surgery. It is not possible to know now if the axillary reverse mapping will prevent lymphedema compared to the usual approach. This study will help the study doctors learn things that will help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- You become pregnant prior to surgery.
- The study is stopped by the Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (NCI). The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this study is to compare usual lymph node surgery to an added procedure during the surgery to help surgeons see the lymph node system better. During usual surgery, the lymph node system may be disrupted, which can cause swelling in the arm. This research study will use a new lymph node surgery technique to look at how fluid drains through the lymph node system in your upper arm. This new procedure could reduce the chance of developing arm swelling. But, it could also cause side effects, which are described in the risks section below.

There will be about 516 people taking part in this study.

This study will help the study doctors find out if this different approach is better than the usual approach. To decide if it is better, the study doctors will be looking to see if the ARM surgery method decreases the risk and or the severity of swelling in the arm and improves your quality of life.

What are the study groups?

This study has 2 study groups; one study group will receive the ARM surgery method and one study group will not receive the ARM surgery method. You will be randomly assigned to one of these two groups. Within these 2 study groups, the exact surgical procedure will differ depending on whether or not you have clinically positive lymph nodes as determined by a physical examination prior to surgery. Having clinically positive lymph nodes means that a doctor can feel or see that one or more lymph nodes near the breast area are swollen during a physical exam, and are suspicious of containing cancer.

- **Group 1 (No axillary reverse mapping)**
  With clinically positive nodes
  If you are in this group, you will have the usual staging surgery for your breast cancer. Your breast cancer surgery will involve removal of a portion of, or all of your breast and removal of lymph nodes in the area of your armpit.

  You will have your arm measurements taken and fill out one questionnaire prior to surgery and then at your 12, 24 and 36-month follow-up visits.

  No clinically positive nodes
  If you are in this group, you will have the usual axillary staging surgery used to treat your breast cancer. Your breast cancer surgery will involve removal of your entire breast and removal of lymph nodes in the area of your armpit. During surgery, your surgeon will look for and remove the lymph nodes that drain from your breast cancer. These are called "sentinel lymph nodes." Your surgeon will use proven methods to help identify the sentinel lymph node.

  The sentinel nodes are then removed and looked at by a pathologist to see if they have cancer. This may happen while you are in surgery. If this sentinel lymph node is negative for cancer, no further lymph node surgery is necessary. If the sentinel lymph node has cancer, you may need to have more lymph nodes in the area of your armpit removed, which is called an axillary lymph node dissection, or "ALND".

  You will also have your arm measurements taken and fill out one questionnaire prior to surgery and then at your 12, 24 and 36-month follow-up visits.

  There will be about 258 people in this group.

- **Group 2 (using axillary reverse mapping)**
  With clinically positive nodes
  If you are in this group, you will get the usual staging surgery for your breast cancer, which is removal of lymph nodes in the area of your armpit. Your breast cancer surgery will involve removal of a portion or all of your breast and removal of lymph nodes in the area of your armpit. During this surgery, you will also get blue dye injected into your armpit to locate the lymph nodes draining from your arm. This is the axillary reverse mapping (ARM) procedure.

You will also have your arm measurements taken and fill out one questionnaire prior to surgery and then at your 12, 24 and 36-month follow-up visits.

No clinically positive nodes
If you are in this group, you will get the usual axillary staging surgery used to treat your breast cancer. Your breast cancer surgery will involve removal of your entire breast and removal of lymph nodes in the area of your armpit. During surgery, your surgeon will look for and remove the lymph nodes that drain from your breast cancer. These are called "sentinel lymph nodes." Your surgeon will use proven methods to help identify the sentinel lymph node. During this surgery, you will also get blue dye injected into your armpit to locate the lymph nodes draining from your arm. This is the axillary reverse mapping (ARM) procedure.

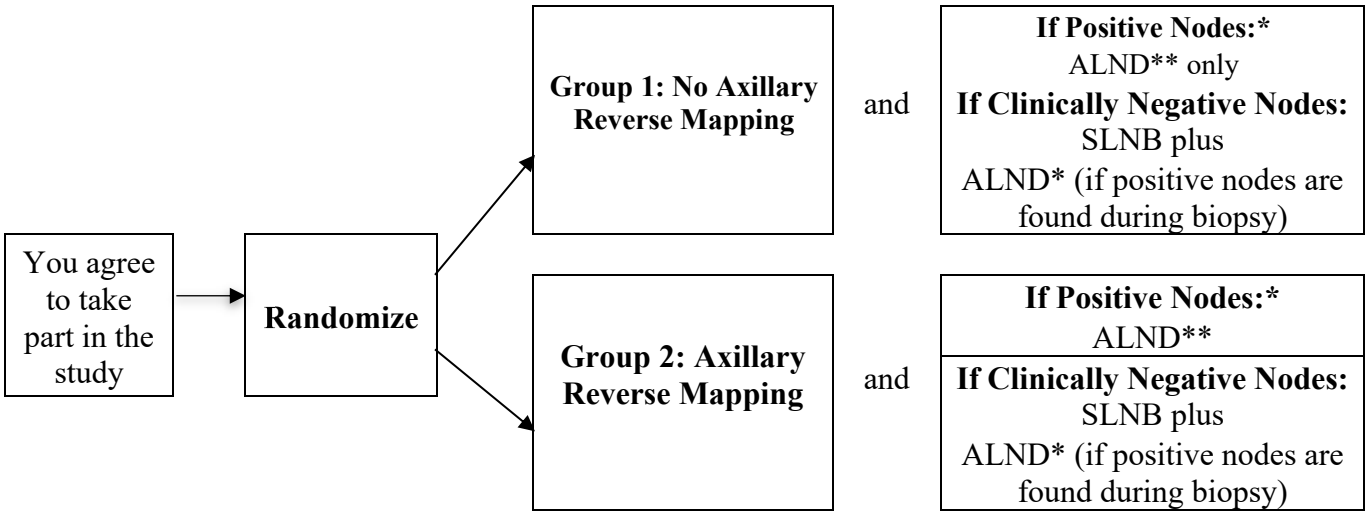
The sentinel nodes are then removed and looked at by a pathologist to see if they have cancer. This may happen while you are in surgery. If this sentinel lymph node is negative for cancer, no further lymph node surgery is necessary. If the sentinel lymph node has cancer, you may need to have more lymph nodes in the area of your armpit removed, which is called an axillary lymph node dissection, or "ALND".

You will also have your arm measurements taken and fill out one questionnaire prior to surgery and then at your 12, 24 and 36-month follow-up visits.

There will be about 258 people in this group.

We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose, and you cannot choose which study group you are in. You will be put into a group by chance. You will have an equal chance of being in Group 1 or Group 2 that is getting the axillary reverse mapping procedure or not.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



* Positive Nodes may be determined by Core Needle Biopsy or by Sentinel Lymph Node Biopsy (SLNB)
** ALND = Axillary Lymph Node Dissection

What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health, but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

These exams, tests, and procedures to monitor your safety and health include:

- Lymphedema assessments (arm circumference measurements) before your surgery.
- History and physical, toxicity assessments at your one month visit after surgery.
- Lymphedema assessments (arm circumference measurements) at your 12, 24 and 36 month follow up visits

If you are an English speaker, and choose to take part in this study, you will be asked to fill out one form with questions about symptoms related to your arm swelling. Researchers will use this information to learn more about how your arm swelling is affecting your quality of life.

Since the forms are being used for research, the responses you provide will not be shared with your study doctor. If you have any serious health issues or other concerns, please talk with your doctor or nurse right away.

You will be asked to fill out this form four times:

- Before your surgery
- At your12, 24 and 36-month follow up clinic visits

Each form may take up to 15 minutes to complete. The forms will ask about things like your physical and emotional well-being, symptoms related to your arm swelling and quality of life. You don't have to answer any question that makes you feel uncomfortable.

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the study approach may not be as good as the usual approach for your breast cancer staging.

If you choose to take part in this study, there are the usual potential risks that are associated with any breast surgery procedure, including bleeding, wound healing, infection, and scar from the incision, as well as risks associated with anesthesia. There is also the risk that adding axillary reverse mapping to your axillary staging procedure may not be any better than the usual axillary staging procedure alone.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The blue dye used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use prior to surgery.

Side Effect Risks

The treatment used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood.

There is also a risk that you could have side effects from the study intervention.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.

You could have side effects from the blue dye used in axillary staging. It can be mildly irritating and the level of discomfort is equal to that of getting blood drawn. The blue dye that is injected may stain the skin in the area of injection for some time. The blue dye will also turn your urine blue for several hours after the surgery and has a small risk of allergic reaction. If a reaction does occur, appropriate treatments will be made available to you.

Drug Risks

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Study Group 1 and Group 2 – If you are in Group 1, you will not have dye injected into your upper extremity, but you may have blue dye injected in your breast if other usual methods for staging do not work. If you are in Group 2, you will be injected with the isosulfan blue dye (Lymphazurin) in your upper extremity.

Possible Side Effects of Lymphazurin (blue mapping dye)

RARE, AND SERIOUS In 100 people receiving Lymphazurin, 3 or fewer may have:
• Serious, potentially life-threatening allergic reaction with respiratory distress, shock, swelling of the lower layer of skin and tissue • Itching • Hives

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

- Keep your study appointments.
- Tell your doctor about:
    - all medications and supplements you are taking
    - any side effects
    - any doctors' visits or hospital stays outside of this study
    - if you have been or are currently in another research study.
- Fill out a form called the "Lymphedema Symptom Intensity and Distress Survey-Arm (LSIDS-A)" before your surgery and at your 12, 24 and 36 month follow up clinic visits.

For women: Do not get pregnant or breastfeed before your surgery. Tell your study doctor right away if you think that you are or have become pregnant.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your breast cancer. This includes:

- the costs of tests, exams, procedures, including surgeries and follow up visits and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- the costs of getting the blue dye ready and giving it to you.
- your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor supporting the study.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research including the Imaging and Radiation Oncology Core (IROC)

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

Where can I get more information?

You may visit the NCI web site at [redacted] for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: [redacted]

A description of this clinical trial will be available on [redacted], 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.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*).

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

My signature agreeing to take part in the study

I have read this consent form, or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study.

Participant's signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature

APPENDIX I: ARM CIRCUMFERENCE MEASUREMENTS

Use the body diagram on paper form to know different measurements for lymphedema.

Reporting Period: *(check one)*

☐ Prior to surgery

☐ 12 month follow-up visit

☐ 24 month follow-up visit

☐ 36 month follow-up visit

Have the lymphedema measurements been performed? *(check one)* ☐Yes ☐No

If No, reason not performed: *(check one)*

☐Patient refusal

☐Site staff forgot to perform

☐Other, specify _____

If Yes, complete the rest of this form including the body diagram

INSTRUCTIONS: If lymphedema measurements have been performed, complete the rest of the form. All measurements should be reported to the nearest tenth of a cm (e.g. 1.3).

Date of measurement: *(dd MMM yyyy)* __ __-__ __ __-__ __ __ __

Side breast cancer surgery performed: (check one) ☐ Right ☐Left

Height __ __ . __ cm

Weight: __ __ __.__ __ kg

BMI __ __ . __ __ *(derived field)*

Was patient diagnosed with lymphedema by measurement since last visit? *(check one)* ☐Yes ☐No

Has the patient reported difficulties with arm lymphedema since the last visit? *(check one)* ☐Yes ☐No

If Yes, treatment/interventions for arm lymphedema:

Exercises ☐Yes ☐No

Compression garment ☐Yes ☐No

Lymphatic massage ☐Yes ☐No

Benzopyrones ☐Yes ☐No

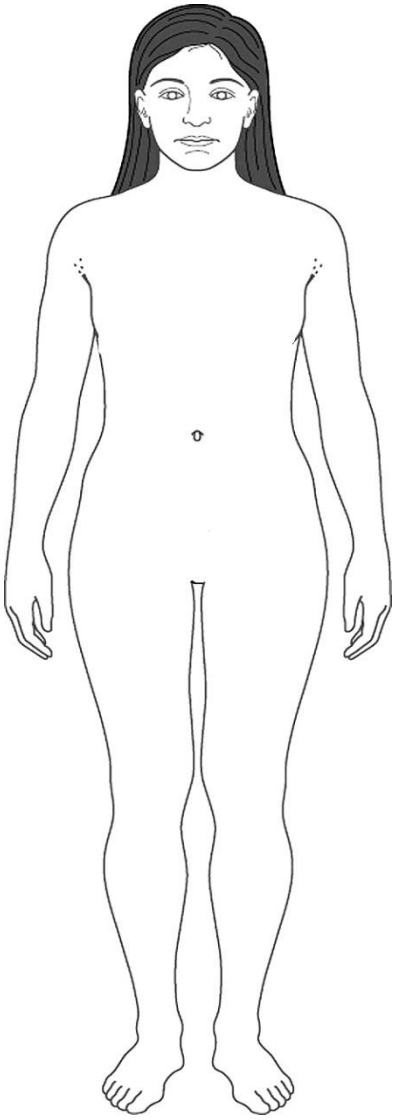
Skin care ☐Yes ☐No

☐Other, specify _____

Body Diagram *(Page 2 of 2)*

INSTRUCTIONS:

1. **Mark an X on the diagram where the breast cancer surgery occurred.**
2. Using a tape measure, obtain arm circumference measurements at the locations indicated below. Measurements should be rounded to the nearest 0.10 cm.
    a. Determine the halfway point distance above and below the antecubital fossa at the baseline visit. Record the distance for reference at future visits. Record the halfway point from antecubital fossa to axilla as the distance above the antecubital fossa. Record the halfway point from antecubital fossa to wrist as the distance below the antecubital fossa. *** Use halfway point measurements documented at Baseline. Do not repeat halfway point measurement at each visit.**
3. Circumferential arm measurements will be completed by the study staff. Open Rave and complete the Arm Circumference Measurements Form.



RIGHT

Halfway point *

Distance above antecubital fossa: __ __.__ cm

Distance below antecubital fossa: __ __.__ cm

Circumference

Axilla: __ __.__ cm

Halfway from antecubital fossa to axilla: __ __.__ cm

Antecubital fossa (just above elbow joint): __ __.__ cm

Halfway from antecubital fossa to wrist: __ __.__ cm

Wrist: __ __.__ cm

LEFT

Halfway point *

Distance above antecubital fossa: __ __.__ cm

Distance below antecubital fossa: __ __.__ cm

Circumference

Axilla: __ __.__ cm

Halfway from antecubital fossa to axilla: __ __.__ cm

Antecubital fossa (just above elbow joint): __ __.__ cm

Halfway from antecubital fossa to wrist: __ __.__ cm

Wrist: __ __.__ cm

APPENDIX II: ABBREVIATIONS

Abbreviations/Definition:

ACOSOG – American College of Surgeons Oncology Group

ALND – Axillary Lymph Node Dissection

ARM – Axillary Reverse Mapping used to identify lymph nodes and lymphatics draining the arm

CTCAE - Common Terminology Criteria for Adverse Events

Crossover node - refers to when the blue node identified by ARM is also the SLN node

IMRT - Intensity Modulated Radiation Therapy

LE – lymphedema

PTV – Planning Target Evaluation

RNI – Regional Nodal Irradiation

SLN(B) – Sentinel Lymph Node (Biopsy) used to identify lymph nodes draining the breast

UE – upper extremity

WBXRT – Whole Breast Radiation