ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE Z11102

Impact of Breast Conservation Surgery on Surgical Outcomes and Cosmesis in Patients with Multiple Ipsilateral Breast Cancers (MIBC)

Clinicaltrials.gov identifier: NCT01556243

[X]	**Update:**	[ ]	**Status Change:**
[ ]	Eligibility changes	[ ]	Activation
[ ]	Therapy / Dose Modifications / Study Calendar changes	[ ]	Closure
[ ]	Informed Consent changes	[ ]	Suspension / temporary closure
[ ]	Scientific / Statistical Considerations changes	[ ]	Reactivation
[X]	Data Submission / Forms changes		
[X]	Editorial / Administrative changes		
[ ]	Other :		

Expedited review is allowed. IRB approval (or disapproval) is required within 90 days. Please follow your IRB of record guidelines.

UPDATES TO PROTOCOL:

Cover page (page 1):
The study document history table has been removed. This table now appears as a separate document on the protocol landing page, on the member side of the Alliance website.

CTSU Contact Information (page 3):
The CTSU Contact Information Table has been updated with the current CTSU boilerplate language.

Protocol Resources (page 4):
-Laura Hoffman has replaced Heather Becker as Protocol Coordinator. All contact information has been updated.
-Tiffany Winter's last name has been updated to Bainter in her name and email address.
- In the table entitled "Protocol-related questions may be directed as follows," the contact name and email address for questions regarding CTEP-AERS reporting has been updated from Regulatory Affairs Manager to Alliance Pharmacovigilance Inbox and from [redacted] to [redacted] respectively. The phone number previously listed for the Regulatory Affairs Manager has been removed as all questions should be submitted via email.

Section 6.1 CTEP Investigator Registration Procedures (page 23):
This section has been retitled "CTEP Registration Procedures" and updated with the current CTSU boilerplate language.

Section 6.2 CTEP Associate Registration Procedures (page 24):
This section has been removed as it is now encompassed within Section 6.1.

Section 6.3 CTSU Site Registration Procedures (page 26):
This section has been renamed "CTSU Registration Procedures" and renumbered as Section 6.2. It has been updated with the current CTSU boilerplate language. All subsequent sections have been renumbered.

Section 6.3.3 Submitting Regulatory Documents (page 25):
This section has been renumbered as Section 6.2.3. The suite number in the CTSU mailing address has been changed to "3000."

Section 10.0 Adverse Event (AE) Reporting and Monitoring (page 40):
All references to "AdEERS" have been replaced with "CTEP-AERS" due to the new CTEP expedited reporting requirements.

Section 10.1 Adverse Event Characteristics (page 40):
-After the first sentence, a second sentence has been added due to the change in CTCAE version for reporting serious adverse events.
-The "4.0" in the third sentence has been changed to "5.0" with regards to the new CTCAE version number used for expedited adverse event reporting.
-The last four sentences have been added to describe the use of CTEP-AERS.

Section 10.11 Adverse Event Monitoring, Data Collection and Reporting (page 40):
-In the fourth sentence of the second paragraph, AdEERS has been replaced with the CTEP-AERS for expedited adverse event reports.
-In the fifth sentence, the phrase "using CTCAE version 5.0" has been added due to the change in CTCAE version requirements for expedited reporting.

Section 10.33 Death (page 42):
-The first four bullets have been deleted.
-The now first bullet point has been replaced with updated CTCAE version 5.0 language.
-Three more bullet points have been added to the end of the section to reflect updated reporting requirements for pregnancy loss and neonatal death in CTCAE version 5.0.

Section 10.34 Secondary Malignancy (page 43):
This section has been replaced in its entirety with the updated CTEP-AERS reporting requirements.

Section 10.4 Expedited Reporting Requirements: Studies Using Commercial Agent(s) ONLY (page 44):
-The sentence beginning with "Refer to 10.41…" under the chart has been removed due to the removal of the 10.41 contact table.
-The sentence beginning with "in the rare event…" has been replaced with a new sentence with updated CTEP contact information.

Section 10.41 (Contact Information for NCI Safety Reporting):
This section has been removed as safety reporting is now done through CTEP-AERS (website URL listed

previously).

Section 16.64 Adverse Events (page 59):
A second sentence has been added to reflect the updated requirement to use CTCAE version 5.0 for expedited adverse event reporting.

UPDATES TO THE MODEL CONSENT FORM:

No updates have been made to the model consent form.

A replacement protocol document has been issued.

This study remains closed to new patient accrual.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Z11102: Impact of Breast Conservation Surgery on Surgical Outcomes and Cosmesis in Patients with Multiple Ipsilateral Breast Cancers (MIBC)

For any communications regarding this protocol, please call the protocol resource person on the following page.

ClinicalTrials.gov Identifier: NCT01556243

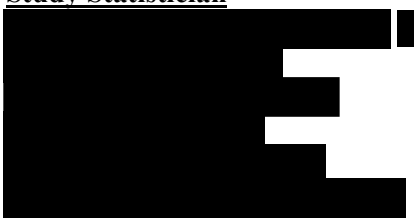
Study Chairs: [redacted]

***Investigator having NCI responsibility for this protocol**

Study Participants	Date Activated
Alliance/Alliance for Clincal Trials in Oncology (lead)	July 23, 2012
ECOG-ACRIN/ECOG-ACRIN Cancer Research Group	November 12, 2012
NRG/NRG Oncology	November 12, 2012
SWOG/SWOG	November 12, 2012

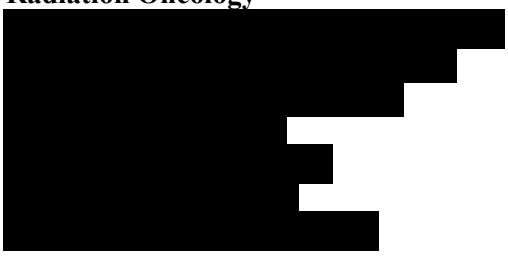
Study Staff

Study Statistician

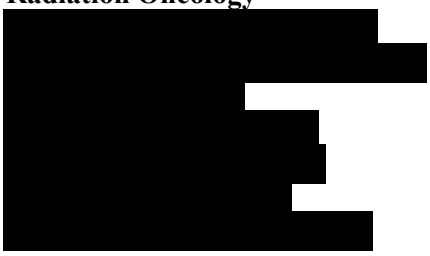


Study Co-Chairs

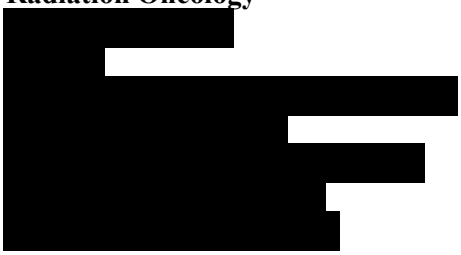
Radiation Oncology



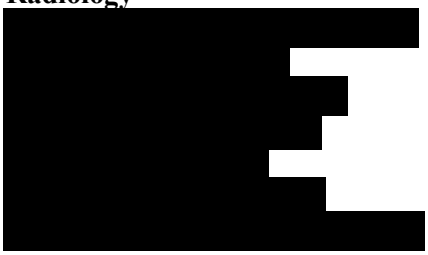
Radiation Oncology



Radiation Oncology



Radiology



Correlative Sciences

√Study contributor(s) not responsible for patient care.

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**Submit study data:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal (Sign in at [redacted] and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at [redacted] Contact the CTSU Help Desk with any OPEN-related questions at [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study Data or forms to CTSU Data Operation. 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 Web page of the CTSU Member website located at [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 user log on with 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 RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) see the Protocol Contacts, Page 4.		
For non-clinical questions (i.e. unrelated to patient eligibility, clinical treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU website is located at [redacted]		

Protocol Resources

Questions:	**Contact Name:**
Patient eligibility*; test schedule; treatment delays, interruptions or adjustments; dose modifications; adverse events; forms completion and submission	[redacted]
Nursing guidelines	[redacted]
Protocol document; consent form; regulatory issues	[redacted]
Radiation quality control	[redacted]
Adverse events (CTEP-AERS; MedWatch; Non-AER and AML/MDS)	[redacted]
Tissue Specimens/Central Specimen Bank	[redacted]

*No waivers of eligibility per NCI

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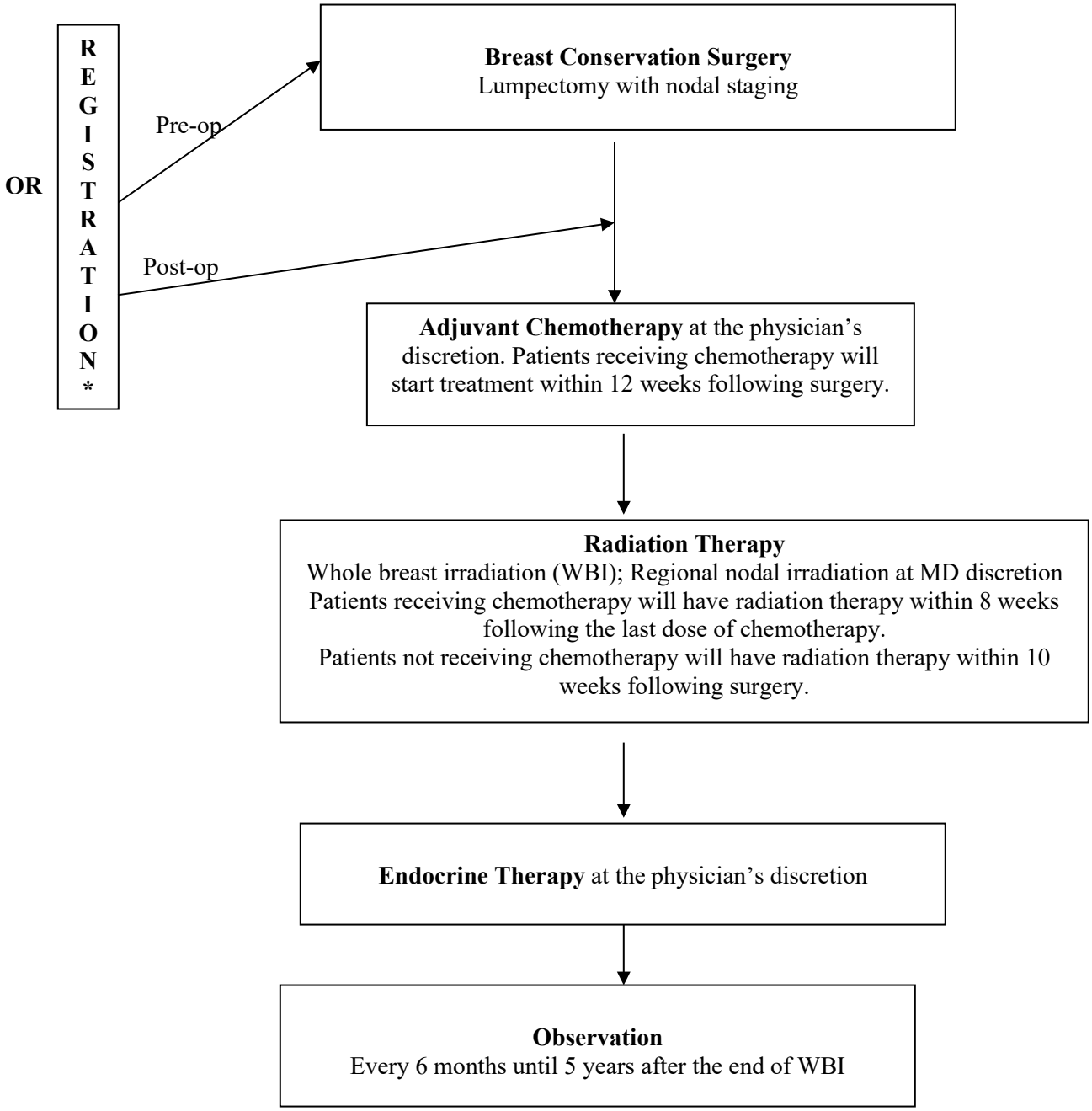
Schema



* Registration can occur prior to surgery OR after surgery (either before or after adjuvant chemotherapy). Registration must occur prior to radiation therapy.

1.0 Background

1.1 Introduction

Over 207,090 women are diagnosed with invasive breast cancer in the United States each year (Jemal *et al*., 2010). An additional 52,000 are diagnosed with ductal carcinoma in situ (DCIS) (American Cancer Society statistics). Of women newly diagnosed with breast cancer, studies have reported that between 14 and 51 percent will undergo preoperative MRI (Arrington *et al*., 2009; Jones *et al*., 2009; Sorbero *et al*., 2009; Wood, 2009). In an era of increasing breast MRI usage and improved radiographic imaging modalities, the incidence of preoperatively identified multiple ipsilateral primary breast cancers (MIBC) including multicentric (MC) and/or multifocal (MF) breast cancer is increasing (Bendifallah *et al*., 2010; Berg and Gilbreath, 2000; Berg *et al*., 2011; Houssami *et al*., 2008; Moon *et al*., 2002; Wilkinson *et al.*, 2005). Data show that MRI is more accurate than mammography alone in detection of MIBC. A meta-analysis performed in 2008 demonstrated that MRI identified additional tumor foci in 16 % of newly diagnosed breast cancer patients (Houssami *et al*., 2008). Increased utilization of bilateral whole breast sonography in women with a new breast cancer diagnosis has also led to increasing detection of MIBC (Wilkinson *et al*., 2005). Other novel imaging modalities, for example positive emission mammography (PEM), breast specific gamma imaging (BSGI) and Molecular Breast Imaging (MBI), may continue to increase the detection of MIBC. A PEM/MRI study reported 14 % of patients enrolled were converted to mastectomy based on findings from these novel images (Berg and Gilbreath, 2000).

The prevalence of MIBC ranges across studies from 13 to 75 % but the true incidence is difficult to ascertain given the varying definitions of multifocal and multicentric used between studies (Bendifallah *et al*., 2010). Classically, multifocal disease is defined as two or more foci of disease within the same quadrant of the breast and multicentric disease as two or more foci of disease in different quadrants of the breast. Differentiating between multifocal and multicentric tumors by the use of quadrants of the breast is not related to tumor biology and is somewhat arbitrary. A tumor at 11 o'clock can be 2 cm away from a tumor at the 1 o'clock position and these would be classified as multicentric, whereas 2 tumors both at the 2 o'clock position that are 5 cm apart may be classified as multifocal. This issue is more pronounced closer to the nipple, where the distance between quadrants is smaller than in the periphery of the breast. The true biologic question is whether women with more than one focus of breast cancer can undergo breast conservation with minimal morbidity and whether local recurrence is equivalent to women with unifocal disease. Therefore, for this study we use the term MIBC defined as two or more foci of biopsy proven breast cancer separated by at least 2 cm of normal breast tissue.

Studies have confirmed that the rate of mastectomy is increasing in the United States (Katipamula *et al*., 2009; McGuire *et al*., 2009). This may be linked to several factors including use of pre-operative MRI and of the resulting increase in detection of MIBC (Bedrosian *et al*., 2003; Bleicher *et al*., 2009; Fischer *et al*., 1999; Lee *et al*., 2004; Morrow and Harris, 209; Touttle *et al*., 2007). Based on historic, retrospective studies from the late 1980s and early 1990s (Kurtz *et al*., 1990; Leopold *et al*., 1989; Wilson *et al*., 1993), most surgeons are reluctant to proceed with breast conservation therapy (BCT) for women with multicentric or multifocal breast cancer due to a perceived high risk of local recurrence (LR). However, no scientific evidence exists to support this increased mastectomy rate in MIBC patients (Fisher, 2011). The emotional impact of mastectomy on body image and quality of life is well documented (Fung *et al*., 2001; Kiebert *et al*.,

1991); Zhao *et al*., 2003). The emotional benefit of breast conservation has driven surgeons in the United States and Europe to recommend breast conservation to over 50 % of women with a single, early stage malignant focus for three decades (Hershman *et al*., 2009; Komenaka *et al*., 2010). BCT is associated with improved patient satisfaction and quality of life and has been shown to be cost effective (Al-Ghazal *et al*., 2000; Barlow *et al*., 2001; Norum *et al*., 1997)

Retrospective studies from the 1980s and early 1990s demonstrated an increased risk of local regional recurrence in women with two or more synchronous lesions in the breast in comparison to women with unifocal cancers treated with breast conservation. However, imaging was less advanced and the margins in the older trial were assessed grossly rather than microscopically (Cho *et al*., 2002; Kaplan *et al*., 2003; Kurtz *et al*., 1990; Leopold *et al*., 1989; Wilson *et al*., 1993)

In contrast, none of the retrospective studies published since 1993 have reported a significant increase in local recurrence rates in women with multicentric/multifocal breast cancer who have been treated with BCT (see Table 1.1) (Cho *et al*., 2002; Gentilini *et al*., Hartsell *et al*., Kaplan *et al*., 2003; Lim *et al*., 2009). Multiple, recent retrospective studies support the safety of breast conservation in women with MIBC and confirm a rate of recurrence that is comparable to rates observed in women with unifocal disease (Bauman *et al*., 2010; Cho *et al*., 2002; Gentilini *et al*., 2009; Hartsell *et al*., 1994). The largest of these contemporary trials, by Gentilini *et al*., reviewed 476 patients with multicentric (12 %) and multifocal (88 %) invasive breast cancer treated between 1997 and 2002. All patients underwent BCT. Despite significant nodal disease in the study population (55 % of all patients), the local recurrence rate in this trial was 5.1 % at 5 years (Gentilini *et al*., 2009). In this study, 98.3 % of the patients received adjuvant systemic therapy with 12.6 % receiving adjuvant chemotherapy alone, 40.1 % hormonal therapy alone, and 45.6 % both chemotherapy and endocrine therapy. Adjuvant whole breast radiation was delivered to 95 %. Also of interest, a retrospective study of women with MIBC treated with neoadjuvant chemotherapy has documented 5 year locoregional failure rates of 7 % in patients with MIBC (Oh *et al*., 2006) .

Table 1.1. Recurrence Rates in Multicentric/Multifocal Breast Cancer by Study

Primary Author of Study	Surgical years	Number of Patients (n)	Median Follow-up (months)	Number of Recurrences	Outcome
Leopold	1968–1981	10	64	4	NA
Kurtz	1975-1983	61	71	15	NA
Wilson	Prior to 12/1988	13	71	3	6 year LRR: 25 %
Fowble	1982-1989	57	48	NA	5 year LRR: 8 %
Hartsell	1977-1989	27	53	1	NA
Cho	1989-1997	15	76	0	NA
Kaplan	1989-2002	36	45	1	NA
Gentilini	1977-2002	476	73	24	Cumulative incidence recurrence at 5 years: 5.1 %
Lim	1990-2003	147	59	3	5 year locoregional recurrence rate: 4.7 %

Table adapted from Bauman *et al*., 2010.

MIBC today includes patients with 2 small foci of disease detected on screening digital mammogram and/or MRI compared to decades ago when MIBC often referred to a palpable mass. Introduction of routine screening mammography and increased patient awareness has led to identification of breast cancer when tumors are smaller in size and early stage breast cancer has better survival compared to more advanced disease. Therefore, more MIBC patients today are eligible for BCT at time of diagnosis due to the smaller tumor size and disease burden, as compared to the 1980s and 1990s when most women with MIBC presented with larger, palpable tumors. Moreover, in women with newly diagnosed breast cancer who undergo MRI for surgical planning, additional malignant lesions which alter the surgical plan (multicentric/multifocal lesions) are detected in 8 to 27 % of patients. This makes it important for us to reassess the indications for BCT versus mastectomy in women with MIBC in 2012.

The European Breast Cancer Conference (EBCC) has recommended standard preoperative breast MRI in all women with newly diagnosed breast cancer given the significant number of additional multicentric/multifocal cancers identified using this modality (6th European Breast Cancer Conference, Berlin, Germany, 15-19 April 2008). In the United States, the role of preoperative breast MRI remains more controversial and as such it is difficult, therefore, to determine how many centers are utilizing routine preoperative MRI. Using a conservative rough estimate of 30% of breast centers utilizing

routine breast MRI (the average of 14 to 51 % documented in the literature (Arrington *et al*., 2009; Sorbero *et al*., 2009) we would expect over 55,000 women with breast cancer to undergo breast MRI for surgical planning. Currently, meta-analysis suggests a 16 % incidence of identification of a second primary in the ipsilateral breast following a cancer diagnosis with further work-up after detection of the initial tumor (Houssami *et al*., 2008). Given the older retrospective case studies in the literature, the majority of surgeons continue to recommend mastectomy for women with multicentric breast cancer and many with multifocal breast cancer. Based on estimates above, over 17,000 women per year will be triaged to mastectomy based on current algorithms.

1.2 Current Study Rationale

1.21 Study Design

While these retrospective data from the modern era described above are encouraging, the safety of BCT in MIBC has not been documented in a prospective fashion. A multicenter study with a uniform and consistent follow-up schedule, defined criteria for recurrence, and strict statistical analysis is necessary to definitively ascertain the safety of breast conservation in the MIBC population. Although an ideal trial design would be a randomized study comparing BCT with mastectomy for women with MIBC, this is felt not to be feasible due to increasing appreciation for shared decision making in the breast cancer population. Discussion with American College of Surgeons Oncology Group (ACOSOG) breast investigators, patient advocates and the Breast Oncology Local Disease (BOLD) taskforce have all indicated that a randomized trial design would not be well supported by patients or physicians. Both patient and surgeon bias would negatively impact timely patient accrual. Therefore, a prospective single arm Phase II trial to address the incidence of local recurrence in women undergoing breast conservation surgery and radiation therapy for MIBC is proposed.

1.22 Prognosis

Controversy exists surrounding the prognosis and treatment of MIBC. No prospective trial has addressed this issue. Limited retrospective data debunk the notion that MIBC is an independent risk factor for worsened overall survival (Bendifallah *et al*., 2010; Pederson *et al*., 2004). A study by Nos *et al*. reviewed 56 women treated with BCT for MIBC in comparison with 132 women who underwent mastectomy for MIBC. In this retrospective study, no differences in overall survival or local recurrence were detected. Similarly, a study by Oh *et al*. reviewed this question in a population of women with clinically detected MIBC treated with neoadjuvant chemotherapy. This study of 706 women treated with mastectomy, mastectomy and adjuvant radiation or breast conservation for MIBC concluded that MIBC does not predict for inferior outcome (Oh *et al*., 2006).

1.23 Tumor Heterogeneity

This trial may also have timely and important translational science implications. Interest in cancer stem cells and tumor heterogeneity is increasing and a better understanding of these concepts may lead to novel diagnostic, therapeutic and

preventive strategies. As has been described in hematologic malignancies, human breast cancers are heterogeneous, both in their pathology and in their molecular profiles (Hwang-Verslues *et al*., 2009; Shipitsin *et al*., 2007) This heterogeneity may be the result of cancer stem cells/progenitor cells which are capable of differentiation along divergent pathways (Nakshatri *et al*., 2009) Heterogeneity exists both within and between breast cancers. The intrinsic heterogeneity in the MIBC population provides an *in vivo* platform to better understand the variation within individual tumors in a given patient but more importantly, between 2 or more tumors in a given patient. This may expand the growing body of knowledge regarding causation of breast cancer, treatments and prognosis.

In an era of individualized medicine, further understanding of the biology of MIBC is required. We have increased understanding of cancer tumor cells and tumor heterogenicity. For women with more than one tumor, understanding whether these tumors are the same or different is important to guide therapy and the correlative science section of this study (see Section 14.0) will evaluate the similarities and differences of multiple foci of disease within the breast.

1.24 Cosmesis

1.241 4-point Scoring System of Breast Cosmesis (Winchester and Cox, 1992)
A single item question will be administered asking both the patient and her surgeon to assess the overall cosmetic result (excellent, good, fair, and poor) (Olivotto *et al*., 1989; Winchester and Cox, 1992). This questionnaire is also being used in the trial NSABP B-39. Olivotto *et al*. also used this single item questionnaire to assess technical factors impacting whether a patient considered the cosmesis a failure following BCT. In general, patients with a fair or poor score are considered to be a cosmetic "failure". Olivotto *et al*. demonstrated that cosmetic scores for patients classified as excellent or good cosmetic score remained consistent after 3, 5, and 7 years in 88 %, 90%, and 78 % of the patients, respectively.

1.242 BREAST-Q©
The BREAST-Q©, a patient-reported outcome (PRO) instrument for breast surgery patients, was recently developed to address the lack of instruments to measure outcome in the breast surgical population (Pusic *et al*., 2009). The questionnaire was developed with strict adherence to guidelines recommended by the Scientific Advisory Committee of the Medical Outcomes Trust and the US Food and Drug Administration (Lohr, 2002; USDHHS, FDA, CDER, CBER and CDRH (2009). This process included development of a conceptual framework, item generation, scale formation with item reduction, and psychometric evaluation. At present, the BREAST-Q© contains three modules (post mastectomy reconstruction, breast reduction and breast augmentation), each with a preoperative and postoperative version. Each module includes six independent scales (satisfaction with breasts, satisfaction with overall outcome, psychosocial well-being, sexual well-being, physical well-being and satisfaction with care). Psychometric evaluation

suggests that it exceeds criteria for rigorous measurement as established by quality of life researchers and government regulatory bodies internationally. More specifically, each scale fulfilled both Rasch and traditional psychometric criteria (including person separation index 0.76 to 0.95; Cronbach's alpha 0.81 to 0.96; and test-retest reproducibility 0.73 to 0.96). The Breast Q was developed using patient interviews, focus groups, expert panels, and a literature review to develop a conceptual framework and a list of questionnaire items.

Current efforts are now underway to develop a fourth module of the BREAST-Q© (the 'Breast-conserving therapy (BCT)' module) to specifically evaluate quality of life in breast cancer patients who undergo BCT. The addition of this new module will allow meaningful comparisons of groups of patients who elect to undergo BCT, mastectomy, or mastectomy with reconstruction. Preliminary versions of the scale have been developed from three sources: review of the literature; qualitative interviews with patients; and expert opinion. Semi-structured, open-ended interviews (n = 30) were recorded, transcribed and analyzed for content. Standard qualitative techniques were then used to identify key domains or themes that emerge. Questionnaire items were developed to reflect these domains and were phrased to reflect terminology and statements typically used by patients. The preliminary measure was then pre-tested in a small sample of patients (n = 20) to clarify ambiguities in the wording of items, and determine acceptability and completion time (personal communication).

Field-testing of this preliminary instrument is now underway (personal communication). Using Rasch analysis, seven measurement criteria will be examined as follows: clinical meaning, thresholds for item response options, item fit statistics, item locations, differential item functioning, correlations between standardized residuals, and person separation index. The aim will be for each scale to consist of a set of clinically meaningful items that satisfy requirements for measurement. This goal will be achieved by choosing a set of items hypothesized to constitute a scale for each area, analyzing the observed data against measurement criteria and making decisions on item selection or deletion. Following item reduction, confirmatory tests on the resultant questionnaire will be performed using traditional psychometric methods in order to enable comparison with existing breast scales and meet regulatory requirements. To this end, five measurement properties will be examined: data quality, tests of scaling assumptions, acceptability, reliability, and responsiveness.

In this study, we will use the independent scales for satisfaction with breasts and satisfaction with overall outcome from the Breast Q© BCT module. Although the final version of the BCT module is still being finalized, the individual questions will not change and no questions will be added, therefore using these questions will enable calculation of a score once the Breast Q© BCT scoring is complete.

1.243 Breast Lymphedema (BLE) Symptom Survey (Degnim *et al*., 2008).

Lymphedema in the ipsilateral arm is a well-recognized complication following breast/axillary surgery, but can also occur in the breast after surgery. We have previously evaluated clinical and surgical factors associated with the development of postoperative breast lymphedema (BLE); yet, BLE diagnosis is currently non-standardized and is based on clinical impression.

Previously, we prospectively evaluated patients undergoing non-mastectomy procedures for signs and symptoms of lymphedema in the operated breast. BLE diagnosis was based on a graded physical exam targeting clinical signs of diffuse skin edema, erythema, and their location. Diagnosis was independent of patient reported symptoms. Additionally, patients also rated symptoms in their operated breast for heaviness, discomfort, redness, visible swelling and associated degree of distress using a 10-point scale ("not at all" = 0 to "a lot" = 10). In subjects with clinical BLE, skin edema and breast erythema were observed in 26/26 (100 %) and 13/26 (50 %), respectively, compared to 5/38 (13 %) and 4/38 (11 %) without clinical BLE, respectively. BLE was observed in more than one quadrant for the majority of patients with BLE (skin edema 18/26 = 69 %, and erythema 10/13 = 77 %). Additionally, BLE patients had significantly higher scores for breast heaviness, discomfort, redness, and swelling and distress associated with these symptoms was significantly elevated only for symptoms of breast heaviness (mean 3.4 vs. 1.0, $p = 0.01$) and discomfort (mean 2.9 vs. 1.4, $p = 0.03$).

Patients undergoing lumpectomy for MIBC and breast radiation with boost to both tumor beds are hypothetically at increased risk of BLE. We will evaluate the incidence of BLE and symptoms as diagnosed using clinical examination along with the same questionnaire used in the previous study to see if BLE is more common in women treated with BCT for MIBC than reported in our previous BLE study evaluating patients undergoing lumpectomy and radiation for unifocal breast cancer.

1.25 Linear Analogue Self-Assessment (LASA)

Both fatigue and overall perception of quality of life will be assessed using LASA. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall quality of life are strong prognostic indicators for survival in cancer patients, independent of performance status (Sloan *et al*., 2009; Tan *et al*., 2008).

2.0 Goals

2.1 Primary Clinical Goal

To assess the local recurrence (LR) rate with breast conservation in patients with multiple ipsilateral primary breast cancer (MIBC).

2.2 Secondary Clinical Goals

2.21 Conversion Rate to Mastectomy

To examine the conversion rate to mastectomy secondary to persistent positive margins; poor cosmesis within the first year of attempting breast conservation surgery (BCS) or inability to satisfy the radiation dose constraints on the boost to the lumpectomy bed of each site of disease.

2.22 Analysis of Patients Without Negative Margins

To assess whether patients who did not undergo re-excision for close margins (< 2 mm) have a higher local recurrence (LR) rate than patients for whom negative margins were achieved.

2.23 Patient's Perception of Cosmesis

To assess patient's perception of cosmesis and incidence of breast lymphedema.

2.24 Incidence of Breast Lymphedema

To assess incidence of breast lymphedema.

2.25 Adverse Effects of Breast Conserving Surgery

To examine the type and severity of adverse effects of breast conserving surgery and radiation for women with multiple ipsilateral primary breast cancer (MIBC).

2.26 Adverse Effects of Whole Breast Irradiation

To examine the radiation-related side effects of whole breast radiation with a boost to 1 large or > 1 lumpectomy site.

2.3 Correlative Goals

2.31 Comparison of Tissue Protein and Gene Expression Patterns

To evaluate protein and gene expression patterns in tissue taken from each breast lesion and to evaluate the concordance of the findings between these lesions.

2.32 Comparison of Imaging and Surgical Findings

To compare the extent of disease described on imaging (mammography, bilateral breast MRI and other adjunctive imaging modalities) with surgical findings.

3.0 Patient Eligibility

3.1 Registration Inclusion Criteria

3.11 Age

Age ≥ 40 years per National Comprehensive Cancer Network (NCCN) recommendations for breast conservation.

3.12 Life Expectancy

Life expectancy of at least 5 years, excluding diagnosis of breast cancer (Comorbid conditions should be taken into consideration, but breast cancer diagnosis is not a consideration)

3.13 Female Gender

Men are excluded from this study. Male breast cancer is a rare event; men are rarely candidates for breast conservation surgery **due to small breast size**. Men are less likely to be candidates for breast conservation surgery if found to have MIBC.

3.14 Foci of Breast Cancer

Upon clinical exam and pre-operative imaging by mammogram +/- MRI, two or three foci of biopsy proven breast cancer separated by ≥ 2 cm of normal breast tissue.
Foci must include ***at least one focus of invasive breast carcinoma*** with ***another focus of either invasive breast carcinoma or ductal carcinoma in situ (DCIS)***.
No more than 2 quadrants with biopsy proven breast cancer.
Note: The shortest distance between lesions must be reported on mammogram +/- MRI and eligibility criteria must be met on both, if both are obtained.
Note: Patient is eligible for study if lesion is not visualized on all imaging modalities (i.e., any of the lesion(s) is/are visualized on MRI but not on mammogram OR visualized on mammogram but not on MRI). Ultrasound cannot be used to determine patient eligibility; eligibility to be determined by bilateral mammogram +/- MRI ***only***. Fine needle aspirate of the second or third lesion to document malignancy is allowed if the first focus is shown to be invasive by core needle biopsy. Patient may remain on study if, upon pathological assessment, two or three lesions identified on pre-operative imaging represent one contiguous lesion.

3.15 Patients may be registered AFTER surgery and PRIOR TO radiation therapy if either of the criteria is met:

1. An area of atypia > 2cm from the index lesion excised at the time of cancer operation is upgraded to DCIS or invasive carcinoma thereby identifying MIBC.

OR

2. Patient underwent resection of two or three foci of malignancy by breast conservation surgery with a minimum of one invasive focus of breast cancer and a minimum of 2 cm of normal breast tissue between the lesions on final pathology.

3.16 Mammogram Imaging

Bilateral mammogram ≤ 90 days prior to date of surgery. **Note:** For patients undergoing more than 1 breast operation, this is the date of the first breast

surgery for breast cancer treatment.

3.17 Staging of Cancer

cN0 or cN1 disease

3.18 ECOG Performance Status (PS)

PS of 0, 1, or 2.
Note: An ECOG PS scale is available on the CTSU website [redacted]

3.19a Ability to Complete Questionnaires

Ability to complete questionnaire(s) by themselves or with assistance.

3.19b Ability to Provide Written Informed Consent

Ability to provide written informed consent.

3.19c Willing to Return to Enrolling Institution

Willing to return to enrolling institution for follow-up during the Active Monitoring Phase (the active treatment and observation portions) of the study. Patients are encouraged to return to the enrolling institution; however, patients may receive radiation therapy at a different institution other than the enrolling institution. Please see Section 7.6 Adjuvant Whole Breast Irradiation (WBI) for more information.

3.2 Registration Exclusion Criteria

3.21 Pregnancy, Nursing and Requirement for Contraception

Any of the following because this study involves radiation therapy (WBI) that has known genotoxic, mutagenic and teratogenic effects:

- Pregnant women
- Nursing women
- Women of childbearing potential who are unwilling to employ adequate contraception (as determined by the treating physician)

3.22 Size of Single Focus of Disease on Preoperative Imaging

Largest single focus of disease > 5 centimeters by either mammogram or MRI or both. **Note**: Measurement of the largest single focus should include any satellite lesions within 1centimeter of the index lesion.

3.23 Prior Staging Procedure

Surgical axillary staging procedure prior to first definitive breast operation. **Note**: FNA or core needle biopsy of axillary node is permitted.

3.24 Evidence of Metastatic Disease

Clinical or radiographic evidence of metastatic disease

3.25 Prior History of Breast Cancer

Prior history of ipsilateral breast cancer [DCIS, LCIS (lobular cancer *in situ)* or invasive]

3.26 Staging of Cancer

cNX, cN2, or cN3 disease

3.27 Breast Implants

Breast implants at time of diagnosis.
Note: Patients who have had implants previously removed prior to diagnosis are eligible.

3.28 Systemic Illnesses or Concurrent Disease

Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would interfere significantly with whole breast irradiation (such as connective tissue disorders, lupus, scleroderma).

3.29a Uncontrolled Intercurrent Illness

Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.29b Bilateral Breast Cancer

Prior or current LCIS, DCIS or invasive breast cancer in the opposite breast (i.e., bilateral disease is not allowed).

3.29c Disallowed Prior Treatments

Treatment including radiation therapy, chemotherapy, biotherapy, hormonal therapy for this cancer prior to surgery (i.e., any neoadjuvant chemotherapy or endocrine therapy is not allowed). Patients who undergo surgical resection with breast conservation and then are treated with adjuvant systemic therapy are eligible to enroll prior to the start of radiotherapy.

3.29d Partial Breast Radiation

Planned partial breast radiation.

3.29e Known BRCA Mutations

Patients with known BRCA mutations. Patients who are not tested or whose testing result is not returned at the time of registration are not excluded from registering to this study.

3.29f Other Active Malignancies

Other active malignancy ≤ 5 years prior to registration.
Exceptions: Non-melanotic skin cancer or carcinoma-in-situ of the cervix.
Note: If there is a history of prior malignancy, they must not be receiving other specific treatment for their cancer.

4.0 Test Schedule

4.1 Test Schedule for Patients Registered Prior to Surgery

Tests and Procedures			Active-Monitoring Phase			
	≤ 60 days prior to registration	At time of registration, prior to surgery	Surgery[6]	Adjuvant Chemotherapy[11]	Radiation Therapy (WBI +/- RNI)[13]	Observation[16]
History and physical exam, including weight, recording of symptoms and medications	X			X	X	
ECOG performance status	X			X[12]	X[14]	
Height	X					
Bilateral mammogram	≤90 days					X[17]
Image submission to IROC Rhode Island (QARC) for central review (see Section 7.0)		X[2]				
Biopsy of each suspicious breast lesion	X					
Adverse event assessment			X[7]		X	
Standard Radiation Treatment Summary submission to IROC Rhode Island (QARC) (see Section 7.0)					X[15]	
Blood samples		X[3]				
Tissue samples			X[8]			
Patient Information Brochures	X[1]					
Baseline Patient Questionnaire Booklet (see Appendix III)		X[4,5]				
Patient Questionnaire Booklet (see Appendix IV)			X[4,9]		X[4,9]	X[5,10]
Surgeon Questionnaire Booklet (see Appendix V)			X[4,10]			

Footnotes for Table 4.1 Test Schedule

1. Patient information brochures are available to give to potential study patients. Brochures can be ordered from CTSU using the order form posted on the CTSU website. Note: CTSU will not send brochures until a site has submitted their IRB approval letter to the CTSU Regulatory Office.

2. The required diagnostic mammograms, along with any optional additional imaging modality (such as MRI, breast ultrasound, BSGI, MBI, PEM, breast tomosynthesis) performed will be submitted to IROC Rhode Island (QARC) for central review. Also, send the reports to the study QAS/Data Manager listed on the Protocol Resources page using the Report Submission Form in Rave. Sites who are not able to scan and attach the reports should contact the QAS/Data Manager for further instructions.

3. For patients who consent, blood collection may be performed within 4 weeks following registration. See Section 14.0 for details.

4. Questionnaire booklets must be ordered from CTSU using the order form posted on the CTSU website. **Note:** CTSU will not send booklets until a site has submitted their IRB approval excerpt to CTSU Regulatory Office.

5. The baseline patient questionnaire booklet will be administered to patients at the time of registration or at any time up to surgery.

6. The first surgical procedures must be performed ≤ 28 days following registration.

7. Adverse events are to be recorded from the start of the first surgery to 30 days after the last surgery performed.

8. For patients who consent, either paraffin-embedded OR frozen tissue will be submitted within 30 days following surgery (see Section 14.0 for details).

9. Active Monitoring patient questionnaire booklets will be administered to patients at the following timepoints: 5 to 30 days following final surgery (initial post-operative visit); every six months (± 1 month) for the first 2 years following completion of WBI; then yearly (± 2 months) for the next 3 years.

10. Surgeon questionnaire booklets will be completed by the patient's surgeon 5 to 30 days following final surgery (initial post-operative visit) to assess cosmetic outcome.

11. Adjuvant chemotherapy is at the discretion of the study physician and should begin within 12 weeks following surgery.

12. Performance status is completed prior to the start and at the end of adjuvant chemotherapy.

13. WBI is performed daily, one session every day, typically Mondays to Fridays for about 6 weeks. See Section 7.6 for details.

14. Performance status is completed prior to the start and at the end of WBI.

15. The radiation plan and standard radiation treatment summary must be submitted to IROC Rhode Island (QARC) for central review. Treatment plan documents are available on the website at [redacted]

16. Observation will be every 6 months (± 1 month) for 5 years beginning at the end of WBI.

17. First observation mammogram should be done at 1 year following completion of WBI, then yearly after that (i.e., at 1, 2, 3, 4 and 5 years, ± 2 months) for a total of 5 years.

4.2 Test Schedule For Patients Registered Following Surgery

Tests and Procedures	Registration	Adjuvant Chemo	Radiation	Observation[7]
History and physical exam, including weight, recording of symptoms and medications	X	X		
ECOG performance status	X	X[5]		
Height	X			
Bilateral mammogram	≤90 days prior to surgery			X[8]
Image submission to IROC Rhode Island (QARC) (see Section 7.0)	X[1]			
Standard Radiation Treatment Summary submission to IROC Rhode Island (QARC) (see Section 7.0)			X[6]	
Research tissue samples	X[2]			
Research blood samples	X[3]			
Patient Questionnaire Booklet (see Appendix IV)		X[4]	X[4]	X[4]

Footnotes for Table 4.2 Test Schedule

1. The required diagnostic mammograms along with any optional additional imaging modality (such as breast ultrasound, MRI, BSGI, MBI, PEM, breast tomosynthesis) performed are required to be submitted. Images and reports should be sent to IROC Rhode Island (QARC) for central review. Also send the reports to the study QAS/Data Manager listed on the Protocol Resources page using the Report Submission Form in Rave. Sites who are not able to scan and attach the reports should contact the QAS/Data Manager for further instructions.

2. For patients who consent, either paraffin-embedded OR frozen tissue will be submitted within 30 days of registration (see Section 14.0 for details).

3. For patients who consent, a blood sample will be submitted within 30 days of registration (see Section 14.0 for details).

4. Questionnaire booklets must be ordered from CTSU using the order form posted on the CTSU website. **Note:** CTSU will not send booklets until a site has submitted their IRB approval excerpt to CTSU Regulatory Office. Patient questionnaire booklets will be administered to patients at the following timepoints:
   every six months (± 1 month) for the first 2 years following completion of WBI; then yearly (± 2 months) for the next 3 years.

5. Performance status is to be assessed prior to the start and at the end of adjuvant chemotherapy, and prior to the start and at the end of WBI.

6. The radiation plan and standard radiation treatment summary must be submitted to IROC Rhode Island (QARC) for central review. Treatment plan documents are available on website at [redacted]

7. Follow-up will be every 6 months (± 1 month) for 5 years beginning at the end of WBI.

8. The first follow-up mammogram should be done at 1 year following the completion of WBI, then yearly after that (i.e., at 1, 2, 3, 4 and 5 years, ± 2 months) for a total of 5 years.

5.0 Stratification Factors/Grouping Factor

None.

6.0 Registration Procedures

6.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) [redacted] Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/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 CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

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

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

6.2 CTSU Registration Procedures

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

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

- In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:
- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

6.2.1 Downloading Site Registration Documents

Site registration forms may be downloaded from the Z11102 protocol page located on the CTSU members' website.

- Go to [redacted] and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the By Lead Organization folder to expand
- Click on the Alliance link to expand, then select trial protocol # Z11102
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided

6.2.2 Requirements for Z11102 Site Registration

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)
- CTSU RT Facilities Inventory Form

NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Image and Radiation Oncology Core(IROC) monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility

6.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

[redacted]

[redacted] (For regulatory document submission only)

6.2.4 Checking Your Site's Registration Status

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

Go to [redacted] and log in to the members' area using your CTEP-IAM username and password

Click on the Regulatory tab at the top of your screen

Click on the Site Registration tab

Enter your 5-character CTEP Institution Code and click on Go

6.3 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 questionnaire booklets are to be ordered prior to the registration of any patients. Patient completed booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the Z11102 website) and faxing the form to the CTSU data operations center at [redacted] Samples of the booklets are found in the Appendices, which are to be used for reference and IRB submission only. They are not to be used for patient completion.

6.4 Patient Registration Procedures

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account [redacted] and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at [redacted] or from the OPEN tab on the CTSU members' side of the website at [redacted]

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

- All eligibility criteria have been met within the protocol stated timeframes.

All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

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 Alliance website for additional

information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at [redacted] For any additional questions contact the CTSU Help Desk at [redacted]

6.5 Registration to Correlative and Companion Studies

6.5.1 Registration to Substudies described in Section 14.0

There are 2 substudies within Alliance Z11102. This correlative science studies **must be offered to all patients** enrolled on Alliance Z11102 (although patients may opt to not participate). These substudies do not require separate IRB approval. The substudies included within Alliance Z11102 are:

- Blood sample, (Section 14.21)
- Tissue Sample, (Section 14.22)

If a patient answers "yes" to "My samples and related information may be used for the additional studies described above," Question #1 in the model consent, they have consented to participate in the substudy described in Section 14. The patient should be registered to the blood sample study at the same time they are registered to the treatment trial (Z11102). Blood sample should be submitted per Section 14.

If a patient answers "yes" to "I agree to provide tissue sample(s) to laboratories associated with Alliance for research testing including genetic sequencing research planned as part of this study," Question #2 in the model consent, they have consented to participate in the substudy described in Section 14. The patient should be registered to the substudy at the same time they are registered to the treatment trial (Z11102). Samples should be submitted per Section 14.3.

6.6 Treating Physician and Site

Treatment on this protocol must commence at an Alliance or CTSU member institution under the supervision of an Alliance or CTSU member physician.

6.7 Start of Study Participation

Study participation will begin either before or after surgery. If registration occurs after surgery patients must be registered prior to radiation therapy.

6.7a Surgery

Patients registered prior to surgery must have surgery ≤ 28 days after registration (see Section 4.0)

6.7b Completion of Tests and Procedures

Tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.7c Grading of Baseline Symptoms

All required baseline symptoms (see Section 10.51) must be documented and graded

6.7d Confirmation of Eligibility

Pre-surgery Registration: A surgeon has seen the patient and confirms the patient is a suitable candidate for this study.

Post-surgery registration: A physician has seen the patient and confirms the patient is a

suitable candidate for this study.

6.7e Questionnaire Booklets Availability
Patient and surgeon questionnaire booklets are available on site; copies are not acceptable for this submission.

7.0 Protocol Treatment

7.1 Preoperative Evaluation Imaging
All patients must have a bilateral diagnostic mammogram prior to registration on this trial (a bilateral breast MRI is optional). Any additional breast imaging modality (i.e., breast sonography, MRI, PEM, BSGI, MBI, breast tomosynthesis or other imaging modality) performed should also be documented and reports and images submitted to IROC Rhode Island (QARC). These reports should also be submitted to the study QAS/Data Manager listed on the Protocol Resources page using the Report Submission Form in Rave. Sites who are not able to scan and attach the reports should contact the QAS/Data Manager for further instructions.

7.11 Bilateral Mammography

The diagnostic mammography should consist of the standard craniocaudal (CC) and mediolateral oblique (MLO) views. Additional spot compression views for mass lesion and magnification views for micro calcifications should be performed, as requested by the interpreting radiologist. The mammographic reports should follow the standardized terminology of the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS ®), in addition to size measurement of the suspicious finding and its distance from the nipple (D'Orsi, 2003). This is part of the data collection forms (lesion size, distance from the nipple and o'clock position in the breast.) Digital mammography is preferred over conventional mammography. All **diagnostic mammogram** images, including images of the computer-aided diagnosis (CAD), and the reports must be submitted to IROC Rhode Island (QARC) for central review. These reports also should be submitted to the study QAS/Data Manager listed on the Protocol Resources Page using the Report Submission Form in Rave. If full field breast tomosynthesis is performed, then the images and report are requested for submission. Sites who are not able to scan and attach the reports should contact the QAS/Data Manager for further instructions.

7.12 Bilateral Breast Magnetic Resonance Imaging (Optional)

MRI requirements described in the Clinical Imaging Guide from the American College of Radiology Accreditation program are highly recommended to ensure adequate coverage of the entire breast and axilla.
[http://www.acr.org/accreditation/Breast-MRI/qc_forms/Clinical-Image-Quality-Guide.aspx. Accessed November 15, 2010.]

The minimum equipment requirements include:

- Dedicated bilateral breast coil.
- Capability of simultaneous bilateral imaging.

- Equipment to perform mammographic correlation, directed breast ultrasound, and MRI-guided intervention, or create a referral arrangement with a cooperative facility for these services.
- Slide thickness of 3 millimeters or less, no gap, in-plane pixel of 1 millimeter or less, and a dynamic series with pre-contrast T1-weighted images followed by at least three post-contrast T1-weight weighted images within 8 minutes of completion of IV contrast injection.

All reporting should have final BI-RADS assessment per ACR BI-RADS-MRI (Ikeda *et al*., 2003).

The MR imaging protocol should contain the minimum sequences recommended by the American College of Radiology listed below:

- T2 images with fat saturation (4-5 millimeter slice thickness),
- Pre-contrast T1 gradient echo images with fat saturation (≤ 2 millimeter slice thickness, no gap),
- Post-contrast T1 gradient echo images with fat saturation (≤ 2 millimeter slice thickness, no gap) with at least two sequences with images obtained immediately after intravenous injection of gadolinium (at T0) and at 3-4 minutes after intravenous injection of gadolinium.

All images including those from the use of computer-aided diagnosis (CAD), pharmacokinetic or other parametric mapping along with reports must be submitted to IROC Rhode Island (QARC) for central review. MRI reports should also be sent to IROC Rhode Island (QARC) and to the study QAS/Data Manager listed on the Protocol Resources Page using the Report Submission Form in Rave. Sites who are not able to scan and attach the reports should contact the QAS/Data Manager for further instructions.

7.13 Additional Imaging

If any other imaging modality is performed (such as whole breast ultrasound, breast specific gamma imaging [BSGI], molecular breast imaging [MBI], positron emission mammography [PEM] or breast tomosynthesis), please submit these images and reports to IROC Rhode Island (QARC) for central review. Reports should also be submitted to the study QAS/Data Manager listed on the Protocol Resources Page using the Report Submission Form in Rave. Submit these images and reports regardless of whether they detected all sites of MIBC or not. Sites who are not able to scan and attach the reports should contact the QAS/Data Manager for further instructions.

7.14 Image-Guided Biopsy and Specimen Radiographs

All suspicious imaging abnormalities (BI-RADS® 4 or 5 lesions) amendable to biopsy should undergo imaged guided biopsy, preferably with clip marker placement at the time of biopsy. Fine needle aspiration or core biopsy is permissible, however, a minimum of one lesion must have core biopsy documenting invasive disease. Submit images of biopsies of each suspicious

lesion. Submit procedure reports and pathology reports from each site biopsy. If specimen radiographs are performed at the time of the surgery, please submit these images as well. The means of diagnosis (percutaneous core or excisional/incisional) will be documented and tracked.

Submit images and the reports from all image-guided biopsies performed (mammogram, ultrasound, MRI, breast-specific gamma imaging (BSGI), PEM, and/or tomosynthesis guided biopsies) with the procedure report and pathology report from the biopsy.

7.15 Central Radiologic Review

The mammograms and any other adjuvant imaging performed will be centrally reviewed using a process that is blinded to the results of the surgery and pathology. If mammograms, breast MRI and other imaging studies were not performed or will not be submitted for technical reasons, notify IROC Rhode Island (QARC) by email at [redacted] Digital files must be in DICOM format and include all image attributes. These files can be submitted electronically via sFTP. Details for obtaining an sFTP account and submission instructions can be found at [redacted] Follow the link labeled digital data. Alternatively, if sFTP is not feasible, the imaging may be burned to a CD and mailed to IROC RI (QARC) at the address below. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Contact IROC RI (QARC) with questions or for additional information.

7.16 Image Submission

Submit required images as follows:

- Diagnostic mammogram images and report
- Diagnostic breast MRI images and reports (if MRI performed)
- Images by any additional imaging (by any modality) and reports
- Image guided biopsy images, procedure report **and** pathology report from the biopsy

Complete and include an Image Submission Checklist with submission to IROC Rhode Island (QARC); checklists may be downloaded from the IROC Rhode Island (QARC) website [redacted]

Send to IROC Rhode Island (QARC) at the address listed on the Protocol Resources page of the protocol.

7.2 Surgery

Patients undergoing breast conserving therapy (BCT) for multiple ipsilateral breast cancers should have all lesions resected to negative margins, either using one lumpectomy or two/three separate lumpectomy incisions at the discretion of the surgeon. Lumpectomy specimens must be oriented and submitted for pathological assessment of margins. Intra-operative confirmation of tumor resection is recommended with intra-

operative specimen radiograph. All sites of biopsy proven malignancy (DCIS or invasive breast cancer) and atypia (atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH) and flat epithelial atypia (FEA)) should be resected at time of surgery.

Primary tumor bed will be defined as the area of invasive and/or DCIS and include nearby small satellite nodules within 1 centimeter of the index lesion.

Each tumor must be resected to negative margins (no tumor at ink).

Re-excision should be done to achieve negative margins as needed. Patients with persistent positive margins should be converted to mastectomy or go off study. For patients who convert to mastectomy within one year of initial surgery, see Section 13.2.

Where possible, surgical clips must be placed to outline the surgical bed for all patients. For patients where an oncoplastic approach to the surgical resection is undertaken, clips must be placed to outline the surgical bed. For the oncoplastic patients, the tissue rearrangement must be clearly documented in the operative report to facilitate radiation planning. Oncoplastic tissue rearrangement by the breast surgeon or plastic surgeon is permitted. Planned autologous tissue flaps (such as latissimus flap, etc.) or implants are not permitted.

Axillary staging is required for all invasive breast cancers with sentinel lymph node (SLN) surgery and/or axillary lymph node dissection (ALND). Completion ALND in the setting of one or two positive sentinel lymph nodes is at the discretion of the treating surgeon. Surgeons are encouraged to perform ALND for patients with three or more positive sentinel nodes or evidence of extra nodal extension in any of the positive sentinel nodes. The status of the axilla will be documented in the trial data collection.

7.3 Pathology

Margin assessment of each lumpectomy specimen is required. For this study negative margin is defined as no tumor at ink. The size of the closest margin should be measured and reported for each lesion. The anterior and posterior margins are excluded from this restriction if the fascia and/or skin are taken.

When 2 or more lesions are excised en bloc, surgical pathology review is required to assess whether the lesions are separate foci of cancer separated by 2 cm or more of healthy breast tissue.

In consenting patients, tissue from each site of disease within the breast will be submitted for tissue banking and correlative science section. Tissue from axillary lymph nodes (sentinel lymph nodes and/or axillary lymph node dissection dependent on case) will also be collected for correlative science evaluation.

Patient may remain on study if, upon pathological assessment, two or three lesions identified on pre-operative imaging represent one contiguous lesion.

7.4 Cosmesis

Following surgery, patients will complete questionnaire booklets at the following time points: 5 to 30 days following final surgery (initial post-operative visit); every six months (± 1 month) for the first 2 years following completion of WBI; then yearly (± 2 months) for the next 3 years following completion of WBI to assess cosmetic outcome. The

patient's surgeon will complete the surgeon questionnaire 5 to 30 days following final surgery (initial post-operative visit) to assess cosmetic outcome. Patients registered after surgery will still complete the questionnaire at the timepoints feasible, based on the timing of their registration.

7.5 Adjuvant Therapy

The use of adjuvant chemotherapy or endocrine therapy will be at the discretion of the treating medical oncologist at the individual institutions based on tumor characteristics. Patients being treated with adjuvant therapy should be treated within 12 weeks following surgery. It is recommended that patients with hormone responsive tumors receive tamoxifen or an aromatase inhibitor. It is recommended that patients with Her2 positive tumors receiving adjuvant chemotherapy receive targeted anti-Her2 therapy.

7.6 Adjuvant Whole Breast Irradiation (WBI)

Patients receiving BCT should receive adjuvant whole breast radiation with a boost to the lumpectomy bed of each site of disease. The boost will be limited to two quadrants of the breast only. **Note:** Patients who cannot or do not receive boost radiation are ineligible and must discontinue the study. The end of study information should be collected and the patient referred to clinical care. Addition of nodal radiation fields will be at the discretion of the treating radiation oncologist.

Patients may receive WBI at an institution other than the enrolling institution. Note that the enrolling institution is responsible for the correct performance of WBI at the other institution and the reporting of all study data. The institution performing WBI must follow all requirements for WBI listed in the protocol, including regulatory requirements such as submission of an RTFI form to CTSU and submission of treatment plans to IROC Rhode Island (QARC).

7.61 Treatment Planning/Delivery

7.611 Three-dimensional CT-based treatment planning is required.

7.612 Heterogeneity corrections are required.

7.613a Intensity modulated radiotherapy (IMRT) with inverse planning is allowed.

7.613b Breath hold technique is allowed

7.614 Optimization with forward planning is allowed.

7.615 Linear accelerators with minimal photon energies of 6MV and electron energies of 6eMEV-20eMEV are required.

7.616 Either electrons or photons may be used for boost treatment.

7.617 Boost treatment to each lumpectomy cavity is required.
Note: Patients who cannot or do not receive a boost are ineligible and must discontinue the study. The end of study information should be collected and the patient referred to clinical care.

7.618 Boost with intraoperative radiotherapy or HDR brachytherapy is not allowed.

7.619 Hypofractionation is not allowed.

7.62 Timing of WBI for Patients Receiving Adjuvant Chemotherapy

7.621 For patients receiving adjuvant cytotoxic chemotherapy, radiation treatment planning and cavity assessment is performed after completion of chemotherapy. WBI should be initiated ≤ 8 weeks after the last dose of cytotoxic chemotherapy. For patients receiving trastuzumab as part of their therapy the trastuzumab can continue during WBI.

7.622 Patients not meeting the dose constraints by 8 weeks after completion of adjuvant cytotoxic chemotherapy should discontinue protocol therapy and are recommended to undergo mastectomy (see Section 13.2).

7.63 Timing of WBI for Patients Not Receiving Adjuvant Chemotherapy

7.631 For patients not receiving adjuvant cytotoxic chemotherapy, radiation treatment planning is to be performed within 6 weeks of lumpectomy (or final operation for re-excision of margins) to determine if the volume of breast tissue receiving 60 Gy is less than or equal to 50% of Breast PTV Eval (see below). If the dose constraint is met, WBI should be initiated by no later than 10 weeks following lumpectomy or re-excision of margins, provided surgical incisions have healed adequately.

7.632 WBI can be carried out concurrently with hormonal therapy; hormonal therapy can be started at any time at the discretion of the treating physician.

7.633 If the dose constraint is not met, patients will be re-scanned no later than 10 weeks after lumpectomy (or final margin re-excision) to allow for cavity shrinkage.

7.634 If the dose constraint is not met within 10 weeks from the last surgery, these patients will discontinue protocol therapy and are recommended to undergo mastectomy, see Section 13.2.

7.365 For patients who are re-scanned at 10 weeks and the dose constraint is met at that time, radiation should start no later than 12 weeks post-surgery.

7.64 Patient Positioning, Immobilization and Imaging

7.641 Simulation CT and treatment delivery should be performed according to institutional standards.

7.642 Radio-opaque markers placed on the lumpectomy incisions, around the palpable breast tissue, and at the borders of the “clinical” tangent fields are often helpful.

7.643 Immobilization using alpha cradle, vac-loc, or breast boards is highly recommended to ensure reproducibility. Prone position is permitted.

7.644 The CT 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 ≤ 0.5 cm should be employed.

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

7.646 The patient may be re-positioned for boost delivery at the discretion of the treating physician.

7.65 Target Volumes

The definitions for the CTV, PTV and normal structures used in this protocol generally conform to the RTOG-endorsed consensus guidelines for delineation of target and normal structures for breast cancer [redacted]

7.651 Breast volumes

7.6511 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 within 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]

7.6512 Breast PTV

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

7.6513 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. This Breast PTV Eval cannot be used for beam aperture generation.

7.652 Lumpectomy volume

7.6521 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. Patients without a clearly identifiable lumpectomy bed are not eligible for protocol participation.

7.6522 Lumpectomy CTV
Lumpectomy GTV + 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.

7.6523 Lumpectomy PTV
Lumpectomy CTV + 3-5 mm 3D expansion (excludes heart).

7.6524 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 5 mm 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.

7.653 Normal Tissues

7.6531 Ipsilateral lung.
This may be contoured with auto-segmentation with manual verification.

7.6532 Contralateral lung.
This may be contoured with auto-segmentation with manual verification.

7.6533 Heart.
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 4 chambers are present. All the mediastinal tissue below this level should be contoured, including the great vessels (ascending and descending aorta, inferior vena cava) and defined as "heart". The heart should be contoured on every contiguous slice thereafter to its inferior most extent near the diaphragm. If one can identify the

esophagus, this structure should be excluded from the heart. One need not include pericardial fat, if present. Contouring along the pericardium itself, when visible, is appropriate.

7.66 Target Dose Fractionation and Dose Prescription

7.661 Whole breast
46-50 Gy in 2 Gy daily fractions or 45-50.4 Gy in 1.8 Gy daily fractions, 5 days a week.
***Per protocol**:* ≥ 95% of the breast PTV Eval will receive ≥ 95% of the prescribed dose. Maximal point dose will be ≤ 115% of the prescribed dose, not including the boost dose.
***Acceptable Variation**:* ≥ 90% of the breast PTV Eval will receive ≥ 90% of the prescribed dose. Maximal point dose will be ≤ 120% of the prescribed dose, not including the boost dose.

7.662 Boost
10-16 Gy in 2 Gy daily fractions, 5 days a week (10 Gy for those receiving 50-50.4 Gy to the whole breast, 14 Gy for those receiving 46 Gy to the whole breast, 16 Gy for those receiving 45 Gy to the whole breast).
***Per protocol**:* ≥ 90% of the lumpectomy PTV Eval will receive ≥ 90% of the prescribed dose. Maximal point dose will be ≤ 115% of the boost prescription dose.

7.663 Accumulative Dose (Whole Breast + Boost)
Per protocol: No more than 50 % of Breast PTV Eval will receive more than 60 Gy.
Acceptable Variation: No more than 60 % of Breast PTV Eval will receive more than 60 Gy.
Every effort should be made to keep no more than 50% of Breast PTV Eval receiving more than 60 Gy, including using 3mm margin for expansion from Lumpectomy CTV to Lumpectomy PTV, and allowing minimum coverage of 90% of the lumpectomy PTV Eval receiving 90% of the prescribed dose.

7.67 Nodal Irradiation

The addition of nodal irradiation is at the discretion of the treating radiation oncologist.

7.671 For those patients with 1-2 positive sentinel lymph nodes (SLNs) not undergoing axillary lymph node dissection, the use of either standard tangent fields or “high tangent fields” covering part or all level II axillary LNs is permitted and is at the discretion of the treating radiation oncologist.

7.672 For those patients with ≥ 3+ SLNs undergoing axillary lymph node dissection, regional nodal irradiation is encouraged, especially in those

with extra capsular extension, nodal ratio > 20 %, high grade disease, and LVSI. Coverage of supraclavicular fossa and high axillary lymph node regions are recommended. Coverage of the internal mammary nodes is at the discretion of the radiation oncologist.

7.673 For those patients with ≥ 3 positive SLNs not undergoing axillary lymph node dissection, regional nodal irradiation is required.

7.674 If regional lymph nodes are treated, contouring of regional lymph nodes per the RTOG breast contouring atlas is required.

7.675 Nodal irradiation dose
Undissected axilla, supraclavicular nodes, internal mammary nodes: 46-50 Gy in 2 Gy daily fractions or 50.4 Gy in 1.8 Gy daily fractions, 5 days a week.

7.68 Dose Limitation for Normal Tissues

7.681 Ipsilateral Lung
Per Protocol: ≤ 30% of the ipsilateral lung should receive ≥ 20 Gy
Variation Acceptable: ≤ 35 % of the ipsilateral lung should receive ≥ 20 Gy

7.682 Contralateral Lung
Per Protocol: ≤ 10% of the contralateral lung should receive 5 Gy or more
Variation Acceptable: ≤ 15% of the contralateral lung should receive 5 Gy or more

7.683 Heart
Per Protocol: ≤ 5% of the whole heart should receive ≥ 25 Gy for left-sided breast cancers, and 0% of the heart should receive ≥ 25 Gy for right-sided breast cancers
Variation Acceptable: ≤ 5% of the whole heart should receive ≥ 30 Gy for left-sided breast cancers, and 0% of the heart should receive ≥ 30 Gy for right-sided breast cancers
Per Protocol: Mean heart dose should be ≤ 400 cGy
Variation Acceptable: ≤ 500 cGy. Every attempt should be made to make the cardiac exposure to radiation as low as possible

7.69a Data Submission

Submission of treatment plans in digital format (either DICOM RT or RTOG format) is required. Digital data must include CT scan structures, dose, and plan files. Submission may be either by sFTP or CD. Instructions for data submission are available on the IROC Rhode Island (QARC) website 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.

7.69a1 Prior to the Start of Radiotherapy
The following data should be submitted prior to the start of radiotherapy:

a. Treatment Planning System Output
   1. RT treatment plan including CT, structures, dose, and plan files. These items are included in the digital plan.
   2. Dose volume histograms (DVH) of target volumes, ipsilateral and contralateral lung and heart. DVH's are included in the digital plan.
   3. Digitally reconstructed radiographs (DRR) for each treatment field.
   4. Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

b. Supportive Data
   1. Prescription Sheet for Entire Treatment

c. Forms
   1. RT-1 Dosimetry Summary Form
      This form is available on the IROC Rhode Island (QARC) website at [redacted]

7.69a2 Within One Week of the Completion of Radiotherapy
The following data should be submitted within one week of the completion of radiotherapy:

a. The RT-2 Radiotherapy Total Dose Record Form
   This form is available on the IROC Rhode Island (QARC) website at [redacted]

b. 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

c. Documentation listed above showing any modifications from original submission.

7.69a3 Supportive data and forms may be included with the transmission of the digital RT data via sFTP or submitted separately via e-mail ([redacted]) or mailed to IROC Rhode Island **(**QARC) at the address listed on the Protocol Resources page of the protocol.

7.69a4 Questions regarding the dose calculations or documentation should be directed to the protocol dosimetrist at IROC Rhode Island (QARC) at the address, email and telephone number listed on the Protocol Resources page of the protocol.

7.69b Quality Assurance

7.69b1 Whole Breast Dose

Variation Acceptable: < 95% of the Breast PTV Eval receives < 95% of the whole breast prescription dose (not including boost dose)

Deviation Unacceptable: < 90% of the Breast PTV Eval receives < 90% of the whole breast prescription dose (not including the boost dose)

Deviation Unacceptable: Maximal point dose is > 120% of the whole breast prescribed dose (not including the boost dose)

7.69b2 Boost Volume Coverage
Deviation Unacceptable: < 90% of the lumpectomy PTV Eval receives < 90% of the boost prescription dose.

7.69b3 Accumulative Breast Dose
Variation Acceptable: Between 50% and 60% of Breast PTV Eval receives more than 60Gy
Deviation Unacceptable: More than 60 % of Breast PTV Eval receives more than 60 Gy.

7.69b4 Volume
Deviation Unacceptable: Whole breast or boost volumes incorrectly defined as deemed by study co-PI.

7.69b5 Critical Organ
The dose to lung or heart-exceeds the protocol's limits specified in Section 7.68

7.7 Patient Follow-up After Completion of WBI
All eligible patients will enter the observation phase of this trial after completion of WBI (see test schedule, Section 4.0). At the follow-up visits, patients will complete a symptom survey and undergo a physical examination. The breast lymphedema symptom survey will assess breast heaviness, swelling, redness, and discomfort. The physical examination will assess the presence or absence of breast edema, which will combine with the symptom score to define cases of breast lymphedema. Lymphedema should be graded using CTCAE version 4.0 (see Section 10.51).

8.0 Dosage Modification Based on Adverse Events

8.1 No Expected Adverse Events
There are no expected adverse events from surgery beyond those related to the standard breast cancer surgery.

8.2 Dose Modifications as per Standard Institutional Practice
Dose modifications for adverse events occurring during physician's choice of adjuvant hormonal or chemotherapy will be managed according to the physician's standard institutional practice.

8.3 Table of Modification of WBI Schedule Based on Adverse Events

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified		
System Organ Class (SOC)	**ADVERSE EVENT**	**ACTION**
Injury, poisoning and procedural complications	Dermatitis radiation, grade 3	Hold WBI treatment for one week or until skin reaction improves to < grade 3.
Any hematologic or non-hematologic adverse event	≥ grade 4	Report to the principal investigator at the time of occurrence.

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

9.0 Ancillary Treatment/Supportive Care

Patients should receive full supportive care while on this study according to institutional standard of care. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. However, CTCAE version 5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. The CTCAE is available at [redacted]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), accessed via the CTEP website, [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. CTEP-AERS reports should be submitted electronically.

10.11 Adverse Event Monitoring, Data Collection and Reporting

Adverse event monitoring, 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 during the trial using Medidata Rave. Additionally, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. Following sections provide information about expedited reporting.

First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). **Important:** Expedited adverse event reporting requires submission of a CTEP Adverse Event Reporting System (CTEP-AERS) report(s). Expedited reports are to be completed using CTCAE version 5.0, within the timeframes and via the mechanisms specified in Section 10.4 and 10.5 All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.4 and 18.0).

10.12 CTCAE and Grade

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to **severity** for the purposes of regulatory reporting to NCI.

NOTE: A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected

- The determination of whether an AE is expected is based on the treatment-specific information provided in Section 15.0 of this protocol.

- Unexpected AEs are those not listed in the treatment-specific information provided in Section 15.0 of this protocol.

NOTE: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite – The adverse event *is clearly related* to the agent(s).
Probable – The adverse event *is likely related* to the agent(s).
Possible – The adverse event *may be related* to the agent(s).
Unlikely – The adverse event *is doubtfully related* to the agent(s).
Unrelated – The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the treatment and the adverse event.

10.31 Special Situations for Expedited Reporting

An expedited report is not required for a specific protocol where an AE is listed as expected. These events must still be reported via routine reporting as specified in Section 10.5. The protocol-specific guidelines supersede the NCI Adverse Event Reporting Guidelines (See Section 10.4) for AE reporting.

10.32 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects,must be reported via CTEP-AERS if they occur at any time following treatment since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.33 Death

Reportable categories of Death

- 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 intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the intervention.

- 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 http://ctep.cancer.gov/). 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.

- In CTCAE v5.0, pregnancy loss is defined as "Death in utero," and 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 CTEP-AERS recognizes this event as a patient death.

- A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

10.34 Secondary Malignancy

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 v5.0, secondary malignancies may be reported as one of the following three options: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy. 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.

10.35 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS.

10.4 Expedited Reporting Requirements: Studies using Commercial Agent(s) ONLY:

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent [1, 2]

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">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" – The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" – A complete expedited report on the AE must be submitted within 7 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 within 3 calendar days for:

- All Grade 4, and Grade 5 Aes

Expedited 7 calendar day reports for:

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

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half- lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

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In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at [redacted] Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically by the original submitter at the site.

10.5 Other Required Expedited Reporting

EVENT TYPE	REPORTING PROCEDURE
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	***NCCTG institutions only:*** Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form within 5 working days of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form. If a CTEP-AERS report has been submitted, this form does not need to be submitted.

10.51 Adverse Events and Symptoms/Conditions to be Graded at Baseline

Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event	Baseline	Each evaluation post-surgery	Each evaluation post WBI
Infections and infestations	Wound Infection		X	X
Injury, poisoning and procedural complications	Dermatitis radiation			X
	Postoperative hemorrhage		X	
	Seroma		X	X
Vascular disorders	Lymphedema	X	X	X

10.52 Adverse Event Submission Using Case Reports Forms (CRFs)

Submit via appropriate Alliance Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.51:

10.521 Grade 2 AEs deemed *possibly, probably, or definitely* related to study surgery or radiation.

10.522 Grade 3 and 4 AEs regardless of attribution to study surgery or radiation.

10.523 Grade 5 AEs (Deaths)

10.5231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to study surgery or radiation.

10.5232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly study related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.53 Submission of Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Diagnosis of Breast Cancer Recurrence and Other Cancer Events

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

11.2 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 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 Second Primary Breast Cancer
Second primary breast cancer is defined histologic evidence of ductal carcinoma *in situ* or invasive breast cancer in the contralateral breast or contralateral chest wall.

11.5 Second Primary Cancer (Non-breast)
Any non-breast second primary cancer other than squamous or basal cell carcinoma of the skin, melanoma *in situ*, or carcinoma *in situ* of the cervix is to be reported and should be confirmed histologically whenever possible.

11.6 Death
Underlying cause of death is to be reported.

12.0 Descriptive Factors

12.1 Menopausal Status
Pre vs. post vs. above categories not applicable (age < or ≥ 50)

- Pre is < 6 months since last menstrual period (LMP) **and** no prior bilateral ovariectomy **and** not on estrogen replacement;
- Post is prior bilateral ovariectomy **or** >12 months since LMP with no prior hysterectomy **and** not currently receiving therapy with LH-RH analogs (e.g., Zoladex))
- Above categories not applicable **and** age < 50
- Above categories not applicable **and** age ≥ 50.

12.2 Time of Registration: Pre-surgery vs Post-surgery

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Follow-Up After Completion of WBI
Patients will be followed as per the test schedule for 5 years after completion of WBI.

13.2 Conditions Requiring Study Termination
Patients who convert to a mastectomy for any reason within a year of initial surgery will go to the observation phase of the study. All data and forms prior to and up to mastectomy must be submitted. Tissue from the mastectomy should be submitted if possible. Patients will be followed for survival yearly for 5 years after treatment discontinuation.

Patients found to have any of the following:

- those with persistent positive margins who decline mastectomy;
- the dose constraint is not met (≤ 10 weeks of initial attempt of WBI planning in patients not receiving adjuvant chemotherapy, or ≤ 8 weeks after completion of chemotherapy for those patients receiving chemotherapy)

will have participation in the study terminated. The on-study material, surgery forms, pathology forms and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is needed.

13.3 Discontinuation After Surgery but Prior to Completion of WBI
Patients who discontinue the study after surgery but prior to completion of WBI due to any of the following:

- patient refusal to undergo or complete WBI;
- physician discretion;
- unacceptable toxicity preventing administration/completion of WBI

will go to the observation phase of this trial; that is, they be followed as per the test schedule for 5 years after treatment discontinuation.

Note: Patients who cannot or do not receive boost radiation are ineligible and must discontinue the study. The end of study information should be collected and the patient referred to clinical care.

13.4 Conditions Requiring Study Discontinuation
Patients who discontinue the study at any time due to any of the following:

- patient refusal to continue study tests and/or procedures
- develop disease recurrence
- administration of anti-neoplastic (non-protocol) treatment

will enter the event monitoring phase where disease and vital status will be collected yearly for 5 years after completion of WBI (or treatment discontinuation).

13.5 Definition of Ineligible
A patient is deemed *ineligible* by the data center if, after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for

study entry.

- If the patient did undergo surgery with/without radiation, submit all treatment/intervention forms and the Off Treatment/Cancel Notification Form.

- If the patient did not undergo surgery, submit on-study material and the Off Treatment/Cancel Notification Form. No further data submission is necessary.

  Note: If, after a site has registered a patient into the study, the site becomes aware of information that questions the patient's eligibility for the study, the site should contact the QAS/Data Manager at the telephone number and/or email address listed on the Protocol Resources page of the protocol.

13.6 Definition of Cancel

A patient is deemed a *cancel* if she withdrew consent prior to surgery. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.7 Recommendations for Local Recurrence

Patients who develop local recurrence are recommended to be evaluated by having a mammogram and MRI and to undergo a mastectomy.

14.0 Biospecimen Submission

14.1 Tissue and Blood Collection Requirements for Correlative Studies

Table 14.1 Summary of Z11102 Tissue and Blood Collection Requirements for Correlative Studies

Biospecimen	Optional/Mandatory	Collection time point	Comment
EDTA whole blood (2 x 10 mL tubes)	**Optional**	Within 4 weeks after registration	
Frozen tissue specimens[1]	**Optional[1]**	Breast conservation surgery	Representative frozen tumor tissue from **each** site of disease, including positive dissected lymph nodes, if applicable ***from the first surgery only*** [2]

Biospecimen	Optional/Mandatory	Collection time point	Comment
Formalin fixed, paraffin-embedded (FFPE) tissue blocks[1]	**Optional[1]**	Breast conservation surgery or at registration if registering after surgery	If it is not logistically possible to procure, freeze, and ship frozen material, one formalin-fixed paraffin-embedded (FFPE) tissue block from **each** site of disease, including positive dissected lymph nodes, if applicable, with a corresponding H&E stained slide from each block ***from the first surgery only***[2,3]

1. For patients registered prior to first surgery either FFPE **OR** frozen tissue specimens will be submitted for patients who consent (both FFPE and frozen are not required). For patients registered after surgery, FFPE specimens should be submitted where available, in patients who consent to the tissue submission.
2. ***For the first surgery only in patients consenting to the tissue submission:*** when selecting a sample for submission, please choose a block or frozen tumor specimen from **each** site of disease with both the greatest amount/area of invasive breast carcinoma/associated stoma and the least amount of non-invasive mammary epithelium (in situ carcinoma, hyperplastic epithelium, normal epithelium). ***Note:*** Operative and pathology reports from all surgeries must be submitted. Tissue specimens from subsequent surgeries are ***not required*** for submission.
3. An alternative submission for FFPE blocks is fifteen 5-micron positive charged slides from **each** site of disease, including dissected, disease-positive lymph nodes, if applicable, with a corresponding H&E stained slide from each block.

14.2 Biospecimen Collections

14.21 Optional Blood Biospecimens

Two 10-mL EDTA tubes of whole blood are requested for correlative studies and for potential future research should the patient consent to giving a blood sample for research purposes.

14.22 Optional Tissue Biospecimens

Either frozen (preferred) **or** FFPE tissue specimens from **each** surgical site of disease and a sample of the intervening non-malignant tissue will be submitted for tissue correlative science evaluation and potentially for future research, should the patient consent. Tissue from axillary lymph nodes (sentinel lymph nodes and/or axillary lymph node dissection dependent on case) will also be collected for correlative science evaluation (see Table 14.1.) **A corresponding H&E slide for each submitted block must be provided** to permit quality assessment of each tissue block.

If frozen tissue cannot be provided, the FFPE tissue block is requested. However, **if an institution is unable to provide a tissue block**, cut fifteen

5-micron positive charged slides. **Label the slides with patient study ID number, pathology accession number, and order in which the sections were cut from the block.** H&E stain the first and last five micron slide that is cut (i.e., slides labeled 1 and 15). These H&E slides will be reviewed centrally for assessing tissue quality. The remaining unstained slides will be processed as described in section 14.4. For samples containing less than 7 square millimeters of tumor tissue, multiple sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. Ideally, each slide must have a minimum of 75 % tumor tissue on the slide to be deemed adequate for study. **Do not bake or place covers slips on the slides.**

14.3 Biospecimen Processing and Submission

14.31 Biospecimen Kits

Blood: Blood specimen kits are required.

Tissue: If an institution is capable of collecting and shipping frozen tissue specimens, kits are strongly recommended and will be provided to each institution on request.

Sites may order these kits **in advance** at no charge from the Alliance-Central Specimen Bank by contacting [redacted] or by email to [redacted] Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.** Kits will arrive inside the shipping boxes. Kits will not be sent via rush delivery service unless the requesting site provides their own FedEx® account number or alternate billing number for express service. **Alliance will not cover the cost for rush delivery of kits.**

14.32 Blood Processing and Submission

Ship two 10 mL EDTA tubes with a properly prepared cold pack. See kit instructions for specific details for cold pack preparation (i.e., frozen or refrigerated) and proper packing of blood and cold pack to avoid freezing of specimen.

14.33 Tissue Processing and Submission

14.331 Frozen Tissue Processing and Submission

After breast conservation surgery, the specimens should be brought to the pathology department as soon as possible (generally speaking, this means within 15 minutes after the time of tissue resection). **If possible, in order to accurately record the *ex vivo* ischemia time, the time at which the specimens are excised from the patient should be recorded.** The specimens should be kept fresh and not put into any type of fixative, although it may be transported to pathology in a solution of normal saline or any other physiologic buffer. The specimens should be reviewed by the attending pathologist or other

authorized individual (pathology resident, fellow, or qualified pathologist assistant). Material needed for diagnosis should be removed and processed according to the institution's standard procedures. Any remaining tissue may be sent to the Alliance Central Specimen Bank.

Where possible, representative and grossly apparent tumor tissue from each foci of disease and one sample of intervening normal breast tissue should be collected. Where two foci of disease are resected in one lumpectomy, non-malignant tissue from the area between the two tumors should also be submitted. Where two separate foci of disease are resected in separate lumpectomies, non-malignant tissue from the area between the two tumors is ***not required*** to be submitted. Normal tissue from the margin of the lumpectomy specimen can be submitted as the intervening normal tissue. Tissue that is grossly necrotic, hemorrhagic or cauterized should be avoided. Tissue should be rapidly divided into segments no larger than 1 cm^3 (1 gram). As many as possible (but at least one) of these sized segments should be collected from **each** site of disease.

If the foci are removed separately and margins on both are negative, it is assumed that the radiographic distance (closest distance by MRI or mammogram) would be the appropriate separation.

Place the tissue segments in the tissue cassettes provided (usually 2-3 segments of tissue per cassette). Use multiple cassettes if necessary - do not “stuff” large amounts of tissue into a single cassette. Label the cassette with 'T' for tumor or 'N' for non-malignant tissue using the marker provided. Wrap each cassette in a piece of foil (provided in the kit). Place the cassette at one end of the foil and roll the foil around the cassette. Carefully fold over the ends of the foil and crease them tightly to create a sealed, compact packet. Immediately immerse the foil-wrapped cassette in liquid nitrogen for 5 minutes. If liquid nitrogen is not available, the specimen may be immersed in an isopentane cryobath available in most surgical pathology frozen section rooms. If using a cryobath, be certain that the temperature of the bath is at or below – 40° C. As a last option, specimens may be frozen by complete immersion in an ethanol / dry-ice bath. Specimens should be left in the cryobath or dry ice bath for at least 15 minutes to ensure complete freezing. Specimens should not be frozen by placing fresh tissue in an – 80° C freezer or inside a cryostat. **The time at which the tissue is frozen should be recorded so that, together with the recorded time of operative resection, the *ex vivo* warm ischemia time can be calculated.**

Once frozen, foil-wrapped tissue cassettes should be placed in one or more of the zip-lock bags provided. Be certain that the specimen bag is accurately and legibly labeled with the patient study ID number. **Once frozen, take extreme care not to let the tissue specimen thaw.** If an ultra-cold freezer (i.e., − 80° C or colder) **is not** available, the specimens must be **shipped the same day they are collected and**

frozen. If an ultra-cold freezer **is** available, specimens may be stored at − 80°C or colder until frozen specimens can be appropriately shipped (≤ 30 days after surgery). The specimens must be shipped with sufficient dry ice for up to two days. **Specimens must remain frozen at all times.**

If resources are not available at the site to collect snap frozen surgical tissue, FFPE tissues must be submitted (see next section).

14.332 FFPE Tissue Processing and Submission

FFPE blocks/slides should be submitted from each of the foci of malignancy and also where available from the intervening non-malignant tissue (as described above). The block/slides must be appropriately packed to prevent damage (i.e., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Tissue specimens must be shipped ≤ 30 days after surgery.

14.34 General Biospecimen Shipping Instructions

Use of the Alliance Biospecimen Management System (BioMS) is mandatory and all specimens must be logged and shipped via this system.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: [redacted] using most standard web browsers such as Internet Explorer, Safari and Firefox. For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs and training videos. To report technical problems, such as login issues or application errors, please contact [redacted] For assistance in using the application or questions or problems related to specific specimen logging, please call [redacted]

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All tissue and blood specimens collected for correlative studies are shipped to the Alliance Central Specimen Bank (CSB) where they will be permanently stored unless a specific request is made to return materials for the purpose of individual patient care or if the patient requests that her materials be returned.

Specimens may be shipped Priority Overnight to the Alliance CSB on Monday through Thursday for next day delivery. The Bank cannot receive specimens on Saturdays, Sundays or holidays. **Do not send specimens on Friday, Saturday or the day before a holiday.**

Sites are responsible for the costs of shipments; however, federal funds for the submission of whole blood and FFPE/frozen tissue specimens are included in the payment schedule and paid upon confirmation of receipt of the specimens.

14.4 Biospecimen Use

14.41 Blood Use

DNA will be extracted from EDTA whole blood and white blood cells will be prepared from residual blood. Similar to the tumor samples being collected in this study (see the following section), DNA will be isolated and subjected to 1) gene expression profiling; 2) array comparative hybridization; and 3) gene sequencing for significantly mutated genes. These studies will be performed in conjunction with the tumor studies.

14.42 Tissue Use

When patients present with multifocal disease, it is unclear whether this represents multiple separate primary cancers or the manifestation of one tumor that has disseminated through the breast to create separate nodules but with similar genomic characteristics. This distinction may have important clinical consequences. Two entirely unrelated cancers arising separately in the same breast could quite logically be treated as separate tumors from the surgical standpoint, but from the medical standpoint may need different systemic approaches. In contrast, tumors that appear separate but are in fact genomically similar may represent wide dissemination of the same malignant process and may not be suitable for conservative breast surgery, but would be treated with the same systemic approach.

To begin to explore this question we will apply genomic approaches, including gene expression, gene copy and gene sequencing to the multiple tumor sites to try to differentiate between these two possibilities. Tumors with similar gene expression profiles, copy number aberrations and somatic mutations will be called related; tumors where these features are discordant will be called unrelated. Clearly one can also envisage the possibility of multi-clonality where two separate nodules have a common precursor but have diverged over time. In this setting, the digital nature of next generation sequencing is very valuable, as not only will we be able to compare a list of mutations, but their frequency, allowing us to study clonality in an efficient way.

These experiments will be conducted in two settings. The first setting is in a subset of patients with three available data sources: 1) have consented to whole genome sequencing; 2) a frozen specimen from each tumor acquired by the surgeon or pathologist; and 3) a germ-line specimen (tube of peripheral blood). This will allow a very deep unbiased genomic analysis and will provide the most definitive data on the relatedness of two separate sites of disease in the breast. The second setting is where one of these three data sources is missing. For patients who did not consent for genomic studies or in whom only fixed material is available or the germline DNA is not available we will use techniques adapted to formalin fixed material to examine selected breast cancer genes for mutation or expression to determine relatedness.

Since this type of analysis has not been attempted before, all statistics will be exploratory; however our primary hypothesis is that unrelated tumors that are

fully excised have a low local recurrence upon breast conservation surgery. In contrast, multiple related tumors will have a high rate of local recurrence because functionally tumors are widely disseminated throughout the breast even though the margins of excision appear negative.

DNA and RNA will be isolated from each separate tumor site and subjected to 1) gene expression profiling (addressing the question of whether the tumor foci have the same or different intrinsic subtype (basal-like, luminal A, luminal B, HER2-enriched, claudin-low); 2) array comparative hybridization (to determine whether they have the same or different patterns of gene copy variation, e.g., LOH and amplification) and 3) gene sequencing. The sequencing will be full genome in a subset of patients where high quality frozen samples were taken and are available from each tumor site. Then in all cases, a sequencing assay for significantly mutated genes in breast cancer can be performed on routinely formalin-fixed tumor material.

Formalin fixed surgical pathology blocks requested to accommodate individual patient management will be returned promptly upon request.

14.5 Return of Genetic Testing Research Results

Because the results generated by the genetic testing described above are not currently anticipated to have clinical relevance to the patient or their family members and will be conducted in a research facility, the genetic results will not be disclosed to the patients or their physicians.

If at any time, incidental genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required prior to reporting any finding. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories or in a setting where a clinical trial is available based on a CLIA laboratory validated sequencing result and the patient has consented to re-contact for additional studies.

15.0 Whole Breast Irradiation (WBI) Risks

15.1 Risks and Side Effects Related to the Whole Breast Irradiation (WBI)

Risks and side effects related to the WBI include the following:

Likely *(Events that occur more than 10 % of the time)*

- Reddening of the skin during treatment and for several weeks following treatment
- Tanning of the skin lasting months and may be permanent
- Slightly smaller breast size or change in the way the breast looks
- Tiredness and weakness during treatment and for several weeks following treatment
- Muscles in chest wall under treated breast may feel tight or sore
- Swelling of breast

Less Likely *(Events that occur 3 to 9 % of the time)*

- Peeling of the skin in the area treated with radiation
- Pain at the site of radiation treatment

Rare but serious *(Events that occur < 3 % of the time)*

- Cough
- Difficulty breathing
- Irritation of the sac surrounding the heart
- Inflammation of the heart muscle
- Rib fracture
- Another cancer due to radiation therapy

16.0 Statistical Considerations and Methodology

16.1 Overview

A single arm phase II clinical trial design will be used to assess whether the local recurrence (LR) rate at 5 years in women with multiple ipsilateral breast cancers who undergo breast conserving surgery is greater than 8 %.

16.2 Study Endpoints

The primary endpoint for this trial is the diagnosis of a local recurrence as a first event where a local recurrence is defined as histologic evidence of ductal carcinoma *in situ* or invasive breast cancer in the ipsilateral breast or chest wall.

The cumulative incidence of local recurrences will be estimated in the competing risk framework as described by Marubini and Valsecchi where regional recurrences, distant recurrences and death without a local recurrence will be considered competing risks and contralateral breast and non-breast second primary cancers will not be considered competing risk.

All eligible patients who have undergone breast conservation surgery with 2 or 3 sites of disease resected to negative margins (i.e., not converted to mastectomy or have not refused mastectomy for positive margins) will be included in the analysis of the primary endpoint.

Secondary clinical endpoints are:

- The conversion rate to mastectomy secondary to persistent positive margins; poor cosmesis within the first year of attempting breast conservation surgery (BCS); or inability to satisfy radiation dose constraints on the boost to the lumpectomy bed of each site of disease

- The type and severity of adverse effects of breast conserving surgery and radiation for women with multiple ipsilateral primary breast cancer (MIBC)

- The radiation-related side effects of whole breast radiation with a boost to 1 large or > 1 lumpectomy site

- The patient's perception of cosmesis.

16.3 Sample Size Determination

Assuming a cohort of 200 eligible patients is enrolled over a 2 year period, the follow-up period after the close of enrollment is 5 years, and the number of local recurrences follows a Poisson distribution, the upper bounds of 95 % confidence interval for the cumulative incidence of a local recurrence within 5 years would fall below 8 % if at most 8 local recurrences occurred as a first event among these 200 patients.

It was originally planned to have an additional 30 patients enrolled to account for patients who withdraw consent prior to surgery, are found to be ineligible after signing a consent form, convert to mastectomy, or are found to have a single contiguous area of malignancy at final pathology. During the course of the study, it was found that many patients were being deemed ineligible after enrollment because the distance between lesions was outside the allowable range. This caused a high rate of ineligibilities. The protocol was amended and the ineligibility rate has subsequently decreased. However, in order to obtain the 200 evaluable patients needed for the primary endpoint, the study will need to enroll a total of 265 (35 additional) patients. Hence the target accrual for the study is 265 patients.

16.4 Accrual Time

American Joint Committee on Cancer (AJCC) version 7.0 defines two macroscopic cancer foci in the same breast as multiple cancers if they are at least 0.5 centimeters apart. No distinction is made as to whether these are multifocal breast cancers (foci no more than 5 cm apart from each other in the same quadrant) or multicentric breast cancers (foci in different quadrants or foci in the same quadrant but more than 5 cm apart from each other). Moreover, the AJCC states that pathologic tumor size should be based only on the single largest tumor and recommends that pathologic T stage be designated as pTany(m) where m indicated the number of multiple lesions. As the presence of multiple ipsilateral breast cancers (MIBC) are not routinely collected through AJCC staging or in the setting of breast cancer clinical trials, the incidence of this disease in general is not well known. Similarly, it is unknown how many women with MIBC have enrolled in clinical trials. Retrospective case studies estimate that 15 % of women diagnosed with breast cancer have MIBC. The estimated number of new female breast cancer cases in 2010 is 207,090 (Jemal *et al*., 2010). Assuming that 15 % of these cases will have multiple ipsilateral breast cancers (31,064 cases) and 3 to 5 % of these multiple ipsilateral breast cancer cases will consider participating in a clinical trial, there will be 932 to 1553 potential candidates for this trial per year. The Alliance investigators accruing to currently open studies are interested and supportive of this trial design. For these reasons, accrual of 8 to 9 patients per month is anticipated to be feasible, for a total accrual time of about 25 months. The study requires and additional 5-6 months of accrual to meet the planned sample size.

16.5 Study Monitoring

16.51 Futility stopping rules

If more than 8 local recurrences are observed as a first event, the trial will stop as the 5 year local recurrence rate is unacceptably high.

A conversion to mastectomy rate of 25 % or more is considered to be unacceptably high. As such, consideration will be given to discontinuing

enrollment if 35 or more women among the first 100 women enrolled convert to mastectomy secondary to persistent positive margins or poor cosmesis within 6 months of BCS. The lower bound for 95 % binomial confidence interval for the conversion rate is 25.7 % (if 35 of 100 women convert to a mastectomy).

16.6 Analysis Plan

16.61 Local Recurrence Rate

All eligible patients who have undergone surgery that was not converted to a mastectomy and who did not have a finding of single contiguous area of malignancy on final pathology will be included in the analysis of the primary endpoint.

The cumulative incidence of local recurrences will be estimated in the competing risk framework as described by Marubini and Valsecchi where regional recurrences, distant recurrences and death without a local recurrence will be considered competing risks and contralateral breast and non-breast second primary cancers will not be considered competing risk. A 95 % Poisson confidence interval for the cumulative incidence of a local recurrence within 5 years will be constructed.

Gentilini *et al.* reported that cumulative incidence of local recurrence differed in terms of estrogen receptor status, HER2/neu expression, Nottingham grade, and Ki-67 expression (univariately) (Gentilini *et al*., 2009). Gray's test will be used to explore whether the cumulative incidence of local recurrence differs with respect to these factors as well as progesterone receptor status, number of positive lymph nodes, number of foci, t-stage, age, perception of quality of life as measured by LASA at registration (poor: 0 to 3; middling: 4 to7; good/excellent: 8 to 10), and fatigue as measured by LASA at registration (none to little: 0 to3; some: 4 to 7; a great deal: 8 to10).

16.62 Conversion to Mastectomy

The conversion rate to mastectomy secondary to persistent positive margins; poor cosmesis within the first year of attempting BCS; or inability to satisfy the radiation dose constraints on the boost to the lumpectomy bed of each site of disease

All eligible patients who have initiated surgery will be included in the analysis of conversion to mastectomy. A 95 % binomial confidence interval will be constructed for the percentage of patients who converted to mastectomy. Logistic regression analysis will be used to assess whether the likelihood of conversion to mastectomy differed with respect to patient and/or disease characteristics.

An interim efficacy analysis will not be performed; final analysis will performed at year 7 after patients have at least 5 years of follow-up.

Patients enrolled subsequent to surgery will be excluded from this analysis.

16.63 Analysis of Patients With Margins <2mm

A subset analysis will be done of patients with close margins (< 2 mm) who did not undergo re-excision.
The purpose is to see whether the inclusion of these patients inflated the local recurrence (LR) rate. In addition, the LR rate of patients with close margins (< 2 mm) who did not undergo re-excision will be estimated with point estimate and 95% confidence interval.

16.64 Adverse Events

The NCI CTCAE version 4.0 will be used to assess the type and severity of adverse effects of breast conserving surgery for women multiple ipsilateral primary breast cancer as well as the type and severity of radiation-related adverse effects of whole breast radiation with a boost to 1 large or > 1 lumpectomy site in women multiple ipsilateral primary breast cancer. However, CTCAE version 5.0 will be used for expedited adverse event reporting.

16.65 Incidence of Breast Lymphedema (BLE)

For each time point, a 95 % binomial confidence interval for the proportion of patients diagnosed with breast lymphedema will be determined. Breast lymphedema will be defined as a patient who has a symptom survey score > 0 and presence of breast edema by physical examination.

16.66 Patient's Perception of Cosmesis

All eligible patients who have undergone surgery that was not converted to a mastectomy will be included in these analyses.

Patient's perception of cosmesis will be assessed at their initial post-operative visit as well as 1, 6, 12, and 24 months following completion of WBI using the BREAST-Q© subscales: satisfaction with breasts, satisfaction with overall outcome, and physical well-being.

Patients registered after surgery will not partake in the pre-operative assessment but will be asked to complete subsequent cosmesis surveys.

The following statistical analyses will be conducted separately for those women who undergo an ALND and those who do not undergo an ALND.

16.661 At Each Time Point
The total score for each of these subscales will be determined using the BREAST-Q© scoring module
[redacted]
For each of the subscales, a 95 % binomial confidence interval for the proportion of patients reporting deficits in that domain will be constructed. Also, a 95 % binomial confidence interval for the proportion of patients indicating that their cosmesis result on the one item questionnaire was poor or fair (scores: 3 or 4) will be constructed. For each of the three subscales, a Wilcoxon rank sum test will be used

to assess domain score differs between those women reporting a poor/fair cosmesis result on the one item questionnaire (scores 1 or 2) and those women reporting a good/excellent cosmesis result on the one item questionnaire.

16.662 Across Time

At years 1 and 2 post WBI, logistic regression modeling will be used to assess which patients, disease, and/or treatment characteristics as well as of breast lymphedema are associated with an increased likelihood of each of the following endpoint: reporting a poor to fair cosmesis, poor satisfaction with breast cosmesis, poor satisfaction with overall outcome, and poor physical well-being.

The agreement between year 1 post WBI cosmesis findings and year 2 post WBI cosmesis findings in terms of a poor to fair cosmesis, poor satisfaction with breast cosmesis, poor satisfaction with overall outcome, and poor physical well-being will be assessed using McNemar tests.

16.663 Agreement with Surgeon's Perception of Cosmetic Results at Initial Post-surgical Evaluation

Impression of cosmesis will be dichotomized as poor to fair versus good to excellent. A 95 % confidence interval will be constructed for the proportion of cases where the patient and his surgeon agree in terms of cosmesis results.

16.664 Differences of the Extent of Disease Described on Mammography Compared with Surgical Findings

All eligible patients who have initiated surgery will be included in the analysis of this endpoint. The maximum lesion dimension and location of each lesion found on mammogram will be determined on central review. Agreement between the lesion size on mammogram and the lesion size reported on surgical pathology report will be examined using the approaches proposed by Bland and Altman. That is, a plot of the average of lesion size on mammogram and the lesion size reported on surgical pathology report versus the difference in lesion size between that found on mammogram and that found on surgery will be constructed to examine systematic biases. A 95 % z-confidence of the difference in lesion size between that found on mammogram and that found on surgery will be constructed. Percent agreement will be used to assess the extent of agreement between location of the lesion seen on mammogram and the location of the lesion reported on surgical pathology report.

16.7 Data and Safety Monitoring

The principal investigator and the study statistician will review the study at least twice a year to identify accrual, adverse event and any endpoint problems that might be developing. The Alliance Data Safety Monitoring Board is responsible for reviewing safety data for this trial at least twice a year, based on reports provided by the Mayo Clinic Cancer Center Statistical Office.

16.8 Inclusion of Women and Minorities

Based on the patient cohort enrolled onto ACOSOG Z1071, we anticipate that the ethnic and racial composition of our study cohort will be as follows:

Racial Categories	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	1	0	0	0	1
Asian	6	0	0	0	6
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	29	0	3	0	32
White	198	0	22	0	220
More Than One Race	5	0	1	0	6
Total	239	0	26	0	265

17.0 Pathology Considerations/Tissue Biospecimens

See Sections 7.0 and 14.0

18.0 Data Collection Procedures

18.1 Medidata Rave

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in the Regulatory Support System (RSS). To access Rave via iMedidata,the site user must have an active CTEP IAM account [redacted] and the appropriate Rave role (RAVE CRA, Read-Only, Site Investigator) on eith the LPO or participating organization roster ate the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login [redacted] using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users 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 link in the upper right pane of the iMediata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at [redacted] or by contacting the CTSU Help Desk at [redacted]

18.2 Submission Timetable

Study phases	
Surgery	Day of the registration to 30 days post the final surgery
Adjuvant chemotherapy	Day of evaluation prior to the start of hormone medications or adjuvant chemotherapy to the day of evaluation following completion of hormone medications or adjuvant chemotherapy
WBI	Day of evaluation prior to the start of WBI to day of evaluation following completion of WBI
Observation[1]	Six months after the completion of WBI to 5 years after the completion of WBI

1. Patients will go to observation for refusal, adverse events or at the discretion of the treating physician. Patients who have recurrence during treatment or during the observation phase and patients who refuse to comply with the test schedule during the observation phase will enter the event monitoring phase (see Section 13.4).

Initial Material(s)

Case Report Form (CRF)	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Institution Contact Information	≤ 2 weeks after registration
On-Study[1]	
On-Study: Mammography	
On-Study: MRI[2] (if performed)	
On-Study: Ultrasound[3]	
On-Study: Biopsy Information	
Adverse Events: Baseline	
Imaging Submission: Institution	
Report Submission[4]	
Reports – Biopsy Procedure, Biopsy Pathology, Mammography and MRI (if performed) Ultrasound (if performed) Note: The distance between the lesions must be documented on mammogram and/or MRI.	
Blood Sample Submission: (Institution)	
Patient Status: Baseline	
Patient Questionnaire Booklet- Baseline	≤ 2 weeks after registration – The Patient Questionnaire Booklet must be ordered by the site using the CTSU request form located on the CTSU website
Patient Questionnaire Booklet - Compliance	≤ 2 weeks after registration - This form must be completed only if the Patient Questionnaire Booklet contains absolutely **NO** patient provided assessment information.
Off Treatment	Submit ≤ 2 weeks after registration if withdrawal/refusal occurs prior to surgery

1. The Breast Lesion Position Diagram must be completed for each patient and uploaded into Rave with the On-Study form. Note: Lesions should be numbered clockwise per the breast diagram completion instructions.
2. This form will be required if an MRI was performed.
3. This form will be required if an ultrasound was performed.
4. This form is used to record the submission of the baseline reports needed for review by the QAS/Data Manager.

Test Schedule Material(s) CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)			
	Surgery Phase	At completion of adjuvant chemotherapy (if applicable)	At completion of WBI	Observation post WBI follow-up
Patient Status: Treatment (Intervention)	X[1]			
Surgery	X[1]			
Contralateral Surgery	X[1, 9]			
Pathology Information	X			
Adverse Event	X		X[1,7]	
Other Adverse Event	X		X[,7,8]	
Patient Questionnaire: Active Monitoring	X[2,3]			X[2,3]
Surgeon Questionnaire: Active Monitoring	X[2,5]			
Patient Questionnaire: Booklet Compliance	X[1]			X[4]
Blood Sample Submission: Institution	X[1]			
Tissue Sample Submission: Institution	X[1]			
Adjuvant Systemic Therapy Evaluation Form		X[6]		
Radiation Treatment Plan Submission			X[7]	
Radiation Therapy Information Form			X[7]	
Start of Adjuvant Endocrine/ Biologic Therapy				X[17]
Patient Status: Clinical Follow Up/Observation				X
Evaluation/Observation				X[10]
Termination of Endocrine Therapy				X[11]
Termination of Biologic Therapy				X[12]
Off Treatment (Completion of WBI)			X	
NCCTG sites only:			At each occurrence (see Section 10.0)	
Notification – Grade 4 or 5 Non-AER Reportable Events/Hospitalization				
Notice of New Primary[13]		At each occurrence	At each occurrence	At each occurrence
Recurrence Information[14]		X	X	X
Local-Regional Recurrence Documentation Submission[15]		X	X	X
Distant Recurrence Documentation Submission[16]		X	X	X

Early Termination of Follow-Up Consent Withdrawal Lost to Follow-Up	These forms must be completed when the study participant is withdrawing consent for QOL (questionnaires), specimens, clinical follow-up only, or all follow-up or if they have become lost to follow-up. These forms are found in the Add Event dropdown list in Rave. Once added, they will be found in the Early Termination of Follow-Up Folder. **Please note:** If the study participant is refusing further study treatment, document the refusal by completing an Off Treatment Form, not a Consent Withdrawal Form.

1. Submit ≤ 30 days following surgery.
2. Patient and surgeon questionnaire booklets must be ordered by the site from the CTSU using the form located on the CTSU website; the forms located in the appendices of the protocol can be downloaded and printed directly from the CTSU website for IRB submission only. Forms used by patients must be ordered from the CTSU.
3. Patient questionnaire booklets will be administered to patients 5 to 30 days following final surgery (initial post-operative visit); every six months (± 1 month) for the first 2 years following completion of WBI; then every year (± 2 months) for the next 3 years to assess cosmetic outcome.
4. This form must be completed only if the Patient Questionnaire Booklet contains absolutely NO patient provided assessment information.
5. Surgeon questionnaire booklets will be completed by the patient's surgeon 5 to 30 days following final surgery (initial post-operative visit) to assess cosmetic outcome.
6. Submit ≤ 30 days following completion/discontinuation of adjuvant chemotherapy.
7. Submit ≤ 30 days following completion/discontinuation of radiation therapy.
8. The Other Adverse Event form is only completed if there are adverse events other than the 'solicited' adverse events.
9. This form is required only if the site indicates on the Surgery form that the patient had surgery to the opposite breast.
10. Complete at each evaluation during observation (See Section 4.0)
11. Complete this form only if patient has ended all adjuvant endocrine therapy.
12. Complete this form only if patient has ended all biologic therapy.
13. If, at any time, the patient has a new primary or contralateral breast disease, complete this form
14. If a recurrence has been reported on the Patient Status form, complete this form
15. If a local-regional recurrence has been reported on the Recurrence Information form, complete this form.
16. If a distant recurrence has been reported on the Recurrence Information form, complete this form.
17. Submit ≤ 30 days following start of adjuvant endocrine therapy.

Follow-up Material(s)

CRF	Event Monitoring Phase[1]				
	every 12 months until PD	At PD	After PD every 12 months	Death	New Primary
Patient Status: Survival and Disease Status Follow Up/Event Monitoring	X	X[2]	X	X	
Recurrence Information[3]		X			
Local-Regional Recurrence Documentation Submission[4]		X			
Distant Recurrence Documentation Submission[5]		X			
Notice of New Primary[6]					At each occurrence
Early Termination of Follow-Up Consent Withdrawal Lost to Follow-Up	These forms must be completed when the study participant is withdrawing consent for QOL (questionnaires), specimens, clinical follow-up only, or all follow-up or if they have become lost to follow-up. These forms are found in the Add Event dropdown list in Rave. Once added, they will be found in the Early Termination of Follow-Up Folder. **Please note:** If the study participant is refusing further study treatment, document the refusal by completing an Off Treatment Form, not a Consent Withdrawal Form.				

1. If a patient is still alive 5 years after the last date of radiation therapy, no further follow-up is required.
2. Submit copy of documentation via the appropriate Recurrence Documentation Submission form in Rave
3. If a recurrence has been reported on the Patient Status form, complete this form.
4. If a local-regional recurrence has been reported on the Recurrence Information form, complete this form.
5. If a distant recurrence has been reported on the Recurrence Information form, complete this form.
6. If, at any time, the patient has a new primary or contralateral breast disease, complete this form.

19.0 Budget

This study is funded by an NIH grant to Alliance.

19.1 Costs Charged to Patient
Routine clinical care

19.2 Tests to be Research Funded
Research blood and tissue sample collection, processing and shipping.

20.0 References

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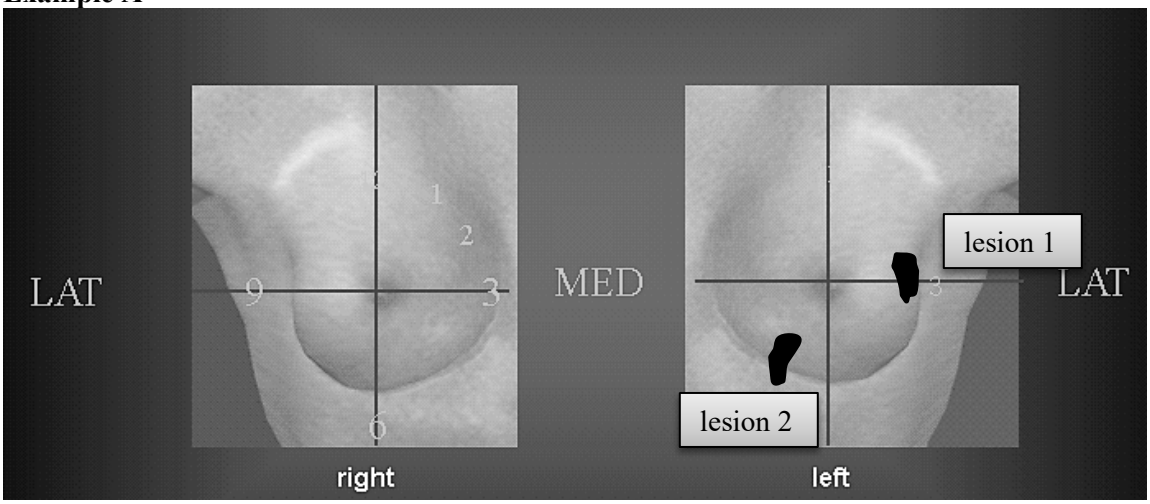
Appendix I: Breast Lesion Position Diagram

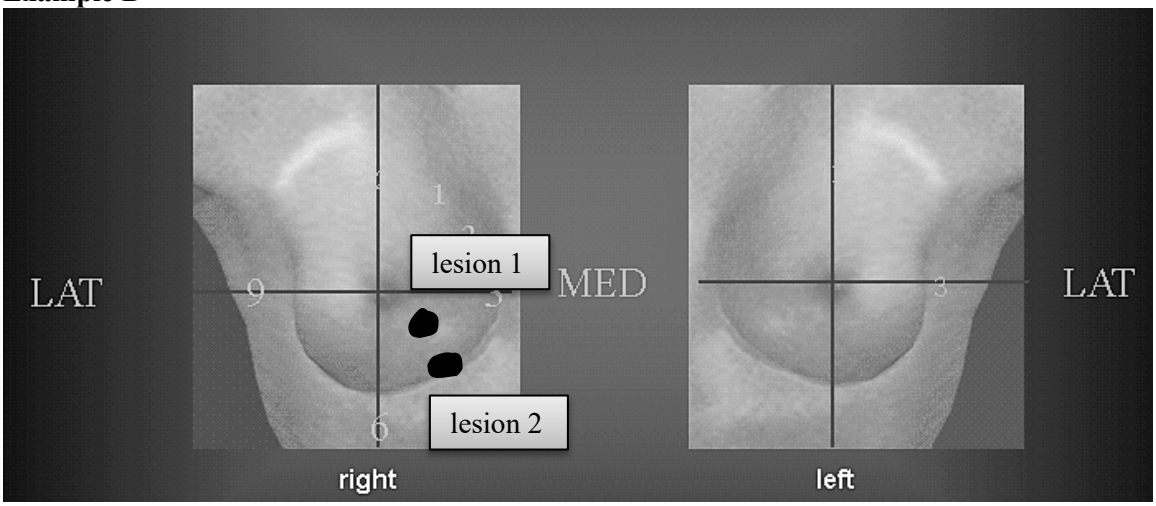
The Breast Lesion Position Diagram is required to document the location of the breast lesions for all patients. The diagram on the following page will be completed by the site investigator and then scanned into Rave by site personnel with data entry capabilities in Rave. Save the Breast Lesion Position Diagram to your computer. Open Rave and look for the field in the Baseline folder, on the On-Study form, named 'Attach Breast Position Diagram Here'. Then select the 'Browse' button to attach the diagram in Rave.

Instructions to site investigator:
On the appropriate side, label all biopsied lesions found to have breast cancer (either DCIS or invasive disease) starting at the 12:01 position and travelling clockwise using the labels lesion 1 and lesion 2 (see Example A). If two lesions are at the same o'clock position, the lesion closest to the nipple should be labeled first then the lesion more distant from the nipple (see Example B).

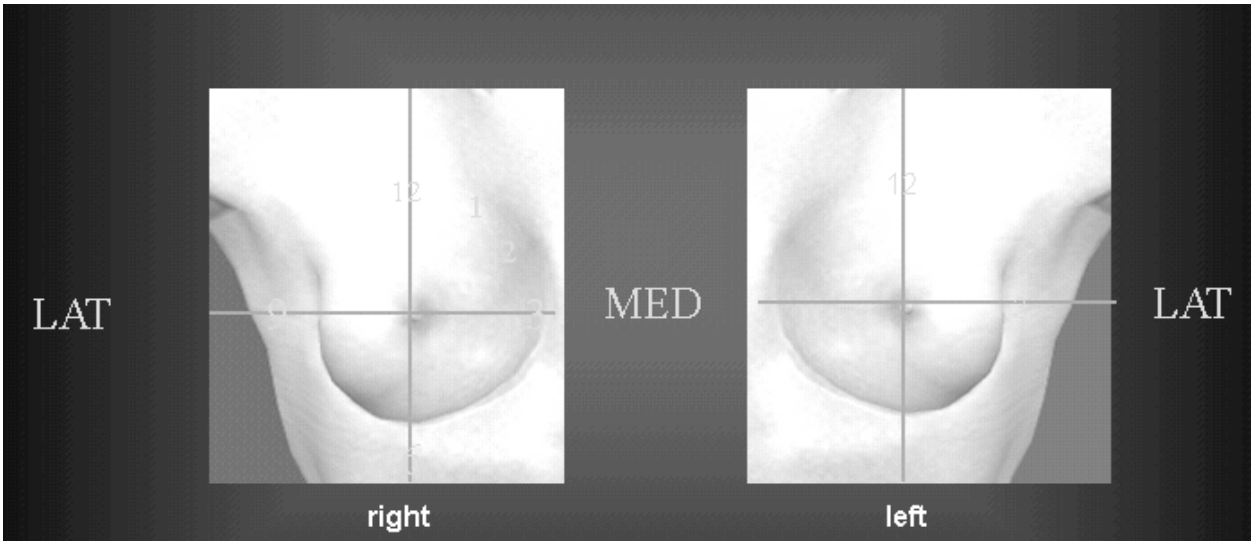
Example A



Example B



Instructions to site investigator:
On the appropriate side, label all biopsied lesions found to have breast cancer (either DCIS or invasive disease) starting at the 12:01 position and travelling clockwise using the labels lesion 1 and lesion 2 (see Example A on previous page). If two lesions are at the same o'clock position, the lesion closest to the nipple should be labeled first then the lesion more distant from the nipple (see Example B on previous page).



Appendix II: Baseline Patient Questionnaire Booklet

PATIENT QUESTIONNAIRE BOOKLET – BASELINE

You have been given a booklet to complete for this study. The booklet contains some questions about your quality of life and health status as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel and tolerate treatment.

1. The booklet contains one set of questions:

   a. Linear Analogue Self-Assessment (LASA) (2 questions)

2. Directions on how to complete the set of questions are written on the top of the set.

3. Please complete the booklet during your scheduled clinic visit and return it to your nurse or your physician.

Thank you for taking the time to help us.

Linear Analogue Self-Assessment (LASA)

Alliance Number: _____ Patient Initials (last, first) _____ Date: _____

Directions: Please circle the one number (0-10) for each item below that best describes you.

How would you describe:

1. your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

2. your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

Appendix III: Patient Information Brochure

Note: The following two pages contain the pink colored patient information brochure available for sites to give to patients should they choose to do so. This brochure is ordered from CTSU. This blank lead page was necessary to ensure that the Table of Contents is correct. Thank you for your patience.

Appendix IV : Active Monitoring Patient Questionnaire Booklet

PATIENT QUESTIONNAIRE BOOKLET – ACTIVE MONITORING

You have been given a booklet to complete for this study. The booklet contains some questions about your cosmetic result, quality of life and health status as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel and tolerate treatment.

1. The booklet contains three sets of questions:
   a. 4-Point Scoring System of Breast Cosmesis (1 question)
   b. BREAST-Q© Breast-conserving therapy (lumpectomy) Postoperative model (54 questions)
   c. Breast Lymphedema (BLE) Symptom Survey (5 questions)

2. Directions on how to complete each set of questions are written on the top of each set.

3. Please complete the booklet during your scheduled clinic visit and return it to your nurse or your physician.

Thank you for taking the time to help us.

4-point Scoring System of Breast Cosmesis

(Winchester and Cox 1992)

Patient Questionnaire

Alliance Number: _____ Patient Initials (last, first) _____ Date: _____

You have been treated with breast conserving therapy for breast cancer. As you know, a reason for choosing this treatment is to keep a breast that looks and feels as close to normal as possible. Your opinion concerning the appearance of your breast is valuable to us. Circle the number next to the word that best describes how your breast looks *now*.

1	When compared to the untreated breast or the original appearance of the breast, there is minimal or no difference in the size or shape of the treated breast. The way the breast feels (its texture) is the same or slightly different. There may be thickening, scar tissue or fluid accumulation within the breast, but not enough to change the appearance.
2	There is a slight difference in the size or shape of the treated breast as compared to the opposite breast or the original appearance of the treated breast. There may be some mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes only a mild change in the shape or size.
3	Obvious differences in the size and shape of the treated breast. This change involves a quarter or less of the breast. There can be moderate thickening or scar tissue of the skin and the breast, and there may be obvious color changes.
4	Marked change in the appearance of the treated breast involving more than a quarter of the breast tissue. The skin changes may be obvious and detract from the appearance of the breast. Severe scarring and thickening of the breast, which clearly alters the appearance of the breast, may be found.

BREAST-Q©
Breast Conservation Therapy (Lumpectomy)
Postoperative Module

Alliance Number: _____ Patient Initials (last, first) _____ Date: _____

The following questions are about your breasts and your breast cancer treatment (by treatment, we mean lumpectomy with or without radiation). After reading each question, please choose the response that best describes your situation. If you are unsure how to answer a question, choose the answer that comes closest to how you feel. Enter only **one** choice per answer. Please answer **every** question. Do not leave any blank.

1. With your breast in mind, in the past 2 weeks, how satisfied or dissatisfied have you been with:

	Very Dissatisfied	**Somewhat Dissatisfied**	**Somewhat Satisfied**	**Very Satisfied**
a. How you look in the mirror clothed?	1	2	3	4
b. The shape of your lumpectomy breast when you are wearing a bra?	1	2	3	4
c. How normal you feel in your clothes?	1	2	3	4
d. Being able to wear clothes that are more fitted?	1	2	3	4
e. How comfortably your bras fit?	1	2	3	4
f. How equal in size your breasts are to each other?	1	2	3	4
g. How normal your lumpectomy breast looks?	1	2	3	4
h. How your lumpectomy breast sits/hangs?	1	2	3	4
i. How soft your lumpectomy breast feels to the touch?	1	2	3	4
j. How much your breasts look the same?	1	2	3	4
k. How smoothly shaped your lumpectomy breast looks?	1	2	3	4
l. The contour (outline) of your lumpectomy breast?	1	2	3	4
m. How your lumpectomy breast looks now compared to before you had any breast surgery?	1	2	3	4
n. How your breasts look in the mirror unclothed?	1	2	3	4
o. How your lumpectomy breast looks overall?	1	2	3	4

2. With your lumpectomy breast in mind, in the past 2 weeks, how much have you been bothered by:

	I don't have this problem	I have this problem and it bothers me…		
		Not at all	A little	A lot
a. Your lumpectomy breast being too small compared to your other breast?		1	2	3
b. Your lumpectomy breast being an irregular shape?		1	2	3
c. Your lumpectomy breast having dimpled (indented) areas?		1	2	3
d. Areas of your lumpectomy breast that look sunken in (hollow)?		1	2	3
e. How obvious your lumpectomy breast scars look?		1	2	3
f. Lack of sensation (feeling) in your lumpectomy breast?		1	2	3
g. Feeling lopsided in your clothing?		1	2	3
h. The nipple and areola on your lumpectomy breast looking caved in?		1	2	3
i. The nipple and areola on your lumpectomy breast moved from its natural position?		1	2	3
j. The nipple on your lumpectomy breast pointing in an unnatural direction?		1	2	3
k. The shape of your areola looking distorted?		1	2	3

3. With your radiated breast in mind, in the past 2 weeks, how much have you been bothered by:

	I don't have this problem	I have this problem and it bothers me…		
		Not at all	A little	A lot
a. Your radiated breast skin looking different (e.g., too dark or too light)?		1	2	3
b. Your radiated areola looking different (e.g., too dark or too light)?		1	2	3
c. Marks on your breast caused by radiation (e.g., small visible blood vessels)?		1	2	3
d. Tattoo marks placed to guide the radiation treatment?		1	2	3
e. Your radiated breast skin feeling dry?		1	2	3
f. Your radiated breast skin feeling sore (sensitive) when touched (e.g., changes in water temperature when you bathe/shower)?		1	2	3
g. Your radiated breast feeling irritated by clothing that you wear?		1	2	3
h. Your radiated breast feeling uncomfortable?		1	2	3
i. Your radiated breast feeling tight?		1	2	3
j. Your radiated breast feeling heavy?		1	2	3
k. Your radiated breast feeling swollen?		1	2	3
l. Your radiated breast feeling unnaturally firm?		1	2	3
m. Hard scar tissue in your radiated breast that you can feel?		1	2	3
n. Your radiated breast skin feeling unnaturally thick (rough, tough) when you touch it?		1	2	3

4. In the past 2 weeks, how often have you experienced?

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Tightness in your lumpectomy breast?	1	2	3	4	5
b. Pulling in your lumpectomy breast?	1	2	3	4	5
c. Tenderness in your lumpectomy breast?	1	2	3	4	5
d. An aching feeling in your lumpectomy breast?	1	2	3	4	5
e. Sharp pains in your lumpectomy breast?	1	2	3	4	5
f. Shooting pains in your lumpectomy breast?	1	2	3	4	5
g. Neck pain?	1	2	3	4	5
h. Upper back pain?	1	2	3	4	5
i. Shoulder pain?	1	2	3	4	5
j. Arm pain?	1	2	3	4	5
k. Difficulty lifting or moving your arms?	1	2	3	4	5
l. Swelling (lymphedema) of the arm on the side that you had your lumpectomy surgery?	1	2	3	4	5
m. Difficulty sleeping because of discomfort in your lumpectomy breast?	1	2	3	4	5
n. Difficulty laying on the side of your lumpectomy breast?	1	2	3	4	5

Breast Lymphedema (BLE) Symptom Survey
(Degnim *et al*. 2008)

Alliance Number: _____ Patient Initials (last, first) _____ Date: _____

Please answer the following questions regarding current (within the last week) symptoms in the operated breast.

1. Does your breast appear or feel swollen?

   Not at all 0 1 2 3 4 5 6 7 8 9 10 A lot

2. Does your breast feel heavy?

   Not at all 0 1 2 3 4 5 6 7 8 9 10 A lot

3. Is your breast redder in color?

   Not at all 0 1 2 3 4 5 6 7 8 9 10 A lot

4. Do you have pain, tenderness, or discomfort in your breast?

   Not at all 0 1 2 3 4 5 6 7 8 9 10 A lot

5. Do you have armpit fullness or numbness?

   Not at all 0 1 2 3 4 5 6 7 8 9 10 A lot

Appendix V: Surgeon Questionnaire Booklet

SURGEON QUESTIONNAIRE BOOKLET

This booklet is to be completed by the surgeon on behalf of the patient prior to completion of the Patient Questionnaire Booklet.

1. The booklet contains the following item:

    - 4-Point Scoring System of Breast Cosmesis (1 question)

2. Directions on how to complete the questionnaire is written on the top of the page.

3. Please complete this booklet prior to the patient's completion of the Patient Questionnaire Booklet corresponding to this visit.

Thank you for taking the time to help us.

4-point Scoring System of Breast Cosmesis
(Winchester and Cox 1992)
Surgeon Questionnaire

Alliance Number: _____ Patient Initials (last, first) _____ Date: _____

Directions: Please circle the score best corresponding to your assessment of your patient's cosmesis.

1	When compared to the untreated breast or the original appearance of the breast, there is minimal or no difference in the size or shape of the treated breast. The way the breast feels (its texture) is the same or slightly different. There may be thickening, scar tissue or fluid accumulation within the breast, but not enough to change the appearance.
2	There is a slight difference in the size or shape of the treated breast as compared to the opposite breast or the original appearance of the treated breast. There may be some mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes only a mild change in the shape or size.
3	Obvious differences in the size and shape of the treated breast. This change involves a quarter or less of the breast. There can be moderate thickening or scar tissue of the skin and the breast, and there may be obvious color changes.
4	Marked change in the appearance of the treated breast involving more than a quarter of the breast tissue. The skin changes may be obvious and detract from the appearance of the breast. Severe scarring and thickening of the breast, which clearly alters the appearance of the breast, may be found.