ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A221505

RT CHARM: PHASE III RANDOMIZED TRIAL OF HYPOFRACTIONATED POST MASTECTOMY RADIATION WITH BREAST RECONSTRUCTION

ClinicalTrials.gov Identifier: NCT03414970

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Study Resources:

Expedited Adverse Event Reporting [redacted]	**Medidata Rave® iMedidata portal** [redacted]
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Protocol-related questions may be directed as follows:

Questions	Contact (via email)
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting	[redacted]
Questions regarding specimens/specimen submissions:	appropriate Alliance Biorepository

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

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

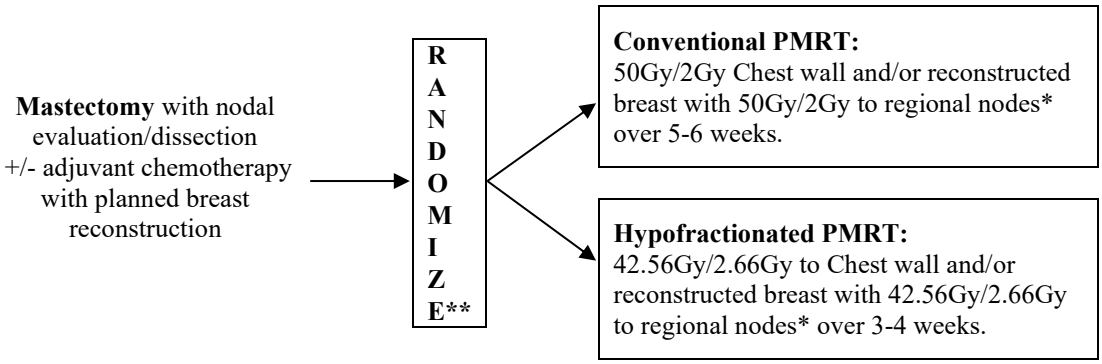
RT CHARM: PHASE III RANDOMIZED TRIAL OF HYPOFRACTIONATED POST MASTECTOMY RADIATION WITH BREAST RECONSTRUCTION

Required Initial Laboratory Values
None

Eligibility Criteria (see Section 3.2)

Histologically confirmed invasive carcinoma of the breast. (See §3.2.1)
Pathologic stage T0N1-2a, T1N1-2a, T2N1-2a, T3N0-2a, all M0 status. (See §3.2.2)
No prior therapeutic radiation therapy to the chest, neck or axilla. (See §3.2.3)
No prior history of ipsilateral breast cancer (invasive disease or DCIS). (See §3.2.4)
No history of prior or concurrent contralateral invasive breast cancer. (See §3.2.5)
No active collagen vascular diseases, such as: systemic lupus erythematous, scleroderma, or dermatomyositis.
Negative inked histologic margins from mastectomy pathology. (See §3.2.7)
No significant post mastectomy complications requiring an unplanned re-operation, or admission for IV antibiotics. (See §3.2.8)
Intent to meet dose constraints. (See §3.2.9)
Radiation oncologist is planning to treat regional lymph nodes including internal mammary nodes.
Radiation oncologist is NOT planning to utilize a chest wall/scar boost.
Patient has undergone breast reconstruction or is planning to undergo reconstruction.
Plan to start radiation treatment within the timeframes specified in Section 7.0
If using tissue expander, no air expander, only fluid filled expanders (See §3.2.13)
For patients with diabetes, hemoglobin A1C test must have been performed ≤ 90 days prior to registration.
No co-existing medical conditions with life expectancy < 5 years.
No other malignancy within 5 years of registration with exception of basal cell or squamous cell carcinoma of the skin. (See §3.2.17)
Negative serum or urine HCG in women of child-bearing potential ≤ 7 days prior to registration (See §3.2.18)
Women of child-bearing potential must agree to utilize a form of birth control or agree to undergo sexual abstinence during radiation therapy.
ECOG (Zubrod) Performance Status 0-1
Patient ≥ 18 years of age
Patients must be able to read and comprehend English, except French patients from CCTG institutions. (See § 3.2.22)

Schema



* Regional Nodes will include axilla (Levels I, II, III), supraclavicular fossa and internal mammary nodes. If an axillary dissection has been performed, RT will only be directed to the un-dissected axilla.

** Patients will be stratified before randomization for immediate versus delayed and autologous versus implant only reconstruction. All reconstruction must be completed before radiation to be classified as immediate and autologous reconstruction is autologous tissue +/- implant.

All patients will undergo reconstruction of the breast; either before or after radiation, but it must be completed within 18 months after finishing radiation therapy, unless medically contraindicated.
Patients will be followed until 15 years after completion of radiation therapy or until death, whichever comes first (§11.3)

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.
There is no surgical credentialing required for participation on this study.

Radiation therapy requires credentialing and submission of patient plans for review. See Sections 7.5 and 14.0 for more detail.

Table of Contents

1.0 BACKGROUND

In the last 5-10 years, there has been a significant shift in the radiation of women with intact breast cancer to shorter, more cost effective and convenient treatment courses. Through the work of several prospective published trials, this concept has been found to be safe and effective in women undergoing breast conserving therapy.[1-4] Decreasing the time required for women to undergo post mastectomy radiation decreases health care costs, and allows patients to spend more time out side of the healthcare setting, ultimately improving patient, employer and payer satisfaction. As the outcomes with traditional post mastectomy are already considered safe and effective, this trial is designed as a non-inferiority trial to ensure that a shorter time course of radiation is as safe as the current standard of care. Although there are limited data from Europe that support this concept in mastectomy and regional nodal irradiation (RNI) patients, no studies have been done in the setting of breast reconstruction. We need prospective randomized data using modern radiotherapy and chemotherapy before widespread adoption occurs here in the United States and elsewhere. Post Mastectomy Radiation Therapy (PMRT) in this setting is a combination of all hypofractionation challenges, combining concerns over adjuvant chemotherapy, post mastectomy chest wall, supraclavicular fossa, internal mammary nodes and reconstructed breast short course radiation. Each of these factors independently is a potential contraindication to hypofractionated radiation due to a lack of data. There are two pressing and currently outstanding questions related to hypofractionation that require resolution in a phase III setting:

1) What is the rate of radiation related complications in reconstructed chest walls treated with shortened course radiotherapy?
2) Is hypofractionation safe when treating regional nodal volumes (where the brachial plexus is located)?

These two questions have been contentious, and their uncertainty will directly affect patient care for years to come, unless a well-designed study can define the unknowns. In this study, both of these questions will be tested and resolved as primary and secondary endpoints. This trial design also collects much needed prospective data regarding the true complication rates for PMRT with breast reconstruction, given the multitude of options for breast reconstruction timing and techniques.

1.1 Rationale for the Study

The primary rationale for accelerated PMRT is the enhanced convenience for patients, which may result in increased access to PMRT. With data now available documenting the low alpha/beta ratio for breast cancer, the fraction sensitivity of breast cancer can be exploited with higher fraction sizes, resulting in more compressed treatment times. We will deliver a dose of 42.56 Gy to the chest wall/reconstructed breast and regional nodes, in 16 daily fractions, 5 days a week. This fractionation should produce late effects and tumor control comparable to a conventionally fractionated course of 50 Gy to the chest wall and regional lymph nodes delivered in 2 Gy daily fractions. No chest wall or reconstructed breast boost will be allowed on this trial. This fractionation scheme has the benefit of delivering the entire treatment over 16 treatment days (weekdays only). This fractionation scheme closely matches that used for breast conservation in the Ontario Clinical Oncology Group and UK Start B trial, as well as the recently closed NRG/RTOG 1005. [2, 3, 5]

As the majority of the radiation oncology community believes that such a fractionation is likely to be equally effective, the key question is that of adverse events, especially in the setting of breast reconstruction. One of the primary supporting trials for this concept is the UK Start B trial. [2] The UK Start B was an accelerated hypofractionation trial comparing 50Gy in 2Gy daily fractions for 5 weeks versus 40Gy delivered in 2.67Gy daily for 15 days. This trial accrued 2215 stage I and II breast cancer patients between 1999 and 2001. Pertinent patient factors in this trial include the fact that 7% of the patients were radiated after mastectomy, 7% received hypofractionated regional nodal radiation and 23% received chemotherapy with or without tamoxifen. The 10 year analysis of this trial demonstrates equivalent local control with local relapse (LR) rate of 5.5% in the 50Gy arm and 4.3% in the 40Gy arm (p=0.21). None of the patients treated in either arm had any reported brachial plexopathy. The UK Start A trial was a precursor trial to Start B, and randomized 2236 early stage breast cancer patients to 50Gy in 25 fractions versus 39Gy or 41.6Gy in 13 fractions over 5 weeks. Contrary to popular conception of

hypofractionation, the 2013 combined analysis of Start A and B demonstrates the late effect to be statistically better in the hypofractionated radiation arms. [5] In the Start A 39Gy arm, moderate or marked breast induration, telangiectasia, and breast edema were significantly less common than the 50Gy arm. In the Start B 40Gy arm, breast shrinkage, telangiectasia, and breast edema were less common that in the 50Gy arm. Given the low adverse event rate of PMRT on the non-reconstructed chest wall, a large sample size would be required to demonstrate superiority (see baseline toxicity). Therefore, we have selected a more frequently seen toxicity in evaluating reconstruction complications to demonstrate non-inferiority of hypofractionation. This method will require significantly fewer participants.

The efficacy of irradiating the chest wall and draining lymph nodes after mastectomy for an improvement in locoregional control has been firmly established by multiple older trials comparing mastectomy alone to mastectomy with postoperative radiation [6-12]. These trials typically used outdated radiation techniques and equipment that produced orthovoltage x-rays. Several trials have studied the efficacy and added benefit of PMRT in the presence of systemic therapy [13-25]. The most definitive of these have come from the Danish Breast Cancer Cooperative Group [21, 22] and the British Columbia Cancer Agency [23]. In addition to these, the updated findings of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis [26, 27], have decisively altered practice and reaffirmed the role of PMRT in modern breast oncology.

The British Columbia trial enrolled 318 node-positive premenopausal breast cancer patients and randomized them after modified radical mastectomy to either radiation therapy or no additional locoregional therapy [23]. Both groups received adjuvant CMF chemotherapy for 12 (first 80 patients) or 6 months. Radiation therapy was hypofractionated and delivered to the chest wall to a dose of 37.5 Gy in 16 daily fractions through opposed tangential photon fields. After a median follow-up of 20 years, the 20-year survival free of locoregional disease developing before systemic was 61% in the chemotherapy alone arm and 87% in the irradiated group. The irradiated group had significantly higher 20-year event-free survival (38% vs. 25%), systemic disease-free survival (48% vs. 31%), breast-cancer specific survival (53% vs. 38%)), and overall survival (47% vs. 37%). There were 3 cardiac deaths (2%) in the irradiated group versus one (0.6%) in the control group ($p=0.62$), and 9% of patients in the irradiated group developed arm edema compared with 3% in the control group ($p=0.035$).

The Early Breast Cancer Trialists' Collaborative Group has collected primary data from every randomized trial of adjuvant radiotherapy in breast cancer, and periodically reports the ongoing analyses on the benefits and risks of radiation therapy in these patients. The most recent report from 2005 reviewed data on 9933 patients enrolled on 25 trials of PMRT, all of which were not confounded by the use of systemic therapy [26]. Node-positive patients who had axillary clearance and received radiation therapy after mastectomy had a 5-year locoregional recurrence rate of 6%, compared to 23% for non-radiated controls (15-year rates were 8% vs. 29%). In a recent 2014 update to the EBCTCG data, PMRT was again evaluated and in all node positive patients found to result in improved local control and disease free survival. [27] In particular, N1 patients the addition of PMRT was found to decrease the 10 yr. local recurrence from 20% to 4% ($p<0.0001$) and improve the 20 yr. breast cancer mortality from 50% to 42% ($p=0.01$).

1.2 Baseline Toxicity from PMRT

In reviewing toxicity data from previous PMRT trials, the Vancouver BC trial reported 9% arm lymphedema (4% needing intervention) and 0.6% symptomatic pulmonary fibrosis. [23]. There was no assessment of cosmesis or reconstruction complications reported in the Danish or Vancouver BC PMRT trials, or the PMRT participants of the UK Start trials. Although not a trial looking at mastectomy patients, the NCIC MA.20, revealed a 7% risk of grade 2 or greater lymphedema in the regional nodal radiation group treated with standard fractionation. [28] With approximately 25% of the Start trial patients undergoing mastectomy, the 5 yr. toxicity data from the hypofractionation arm of 40Gy in 15 fractions in the Start B trial reported the following:

Symptomatic rib fracture	2%
Lung fibrosis	1.7%
Ischemic heart disease	1.5%
Brachial plexopathy	0%
Breast edema	5%
Telangiectasia	1.8%
Arm stiffness	3%
Arm Lymphedema	3%

Based on this information, we feel that a reasonable expected combined grade 2 or greater non-acute toxicity rate would be 7-10%, a conservative estimate as many trials (including NCIC MA.20) have concluded that the risk of grade 2 lymphedema alone to be at least this high with regional nodal RT. In the next section, the 2014 updated analysis of Start A and B is discussed with results suggesting that toxicity from hypofractionation may actually be superior to conventional fractionation.

Research has found that PMRT is an independent risk factor for complications in patients undergoing breast reconstruction. Radiation-associated complications include infection, seroma, delayed wound healing, capsular contracture, implant removal, fat necrosis and poor cosmetic results. A recently published claims-based review evaluated the complications for 14,894 reconstructed patients with an average age of 54. [29] They found a rate of 5-10% wound healing difficulty, 20% infection, 25% implant removal and 16% fat necrosis (autologous). These numbers included patients undergoing both implant and autologous reconstruction, with and without radiation therapy (RT), and RT was associated with an increased risk of infection, implant removal and fat necrosis. To ensure a sufficient event rate, we've selected a conservative composite reconstruction event rate of 25% in our standard treatment arm. Reflecting the heterogeneity of breast reconstruction practiced in the country, in this trial we plan to allow a variety of reconstruction techniques, given the controversy over superiority in the literature: immediate or delayed implants, autologous tissue, or a combination of both. We also plan to allow the use of acellular dermal matrix or similar soft tissue augmentation matrices.

Benediktsson et al. 2006[30]	107 pts. PMRT & Immediate reconstruction, saline prosthesis	41.7% Baker 3 or 4 contracture	
Christante, et al. 2010[31]	100 pts. PMRT & Immediate breast reconstruction	44% complications and 31% required implant removal	Delayed reconstruction patients had only a 22% complication rate
Cordeiro et al. 2004[32]	159 pts. Recon before RT	68% contracture with 80% patient good cosmesis	
Alderman, et al. 2002[33]	326 pts. PMRT, 12 centers	52% complications in immediate reconstruction	Delayed reconstruction rate 33%
Whitfield, et al. 2008[34]	42 pts. PMRT implants or TEs, 40Gy in 15 fractions	19.5% revisional surgery for capsular contracture	
Jhaveri, et al. 2008[35]	92 pts. PMRT and Immediate recon	25% rate of severe complications (Surgery or IV antibiotics)	0% complication autologous tissue recon
Fowble, et al. 2015[36]	99 pts. Immed TE and PMRT	18% failure rate 3.8 yrs.	

1.3 Altered Fractionation in Breast Cancer

In standard chest wall irradiation, daily fraction sizes of 180 cGy or 200 cGy are commonly used and are described as conventional or standard. The rationale for conventional fractionation and the relationship between fraction size and tissue response is well described by the α/β ratio in the linear quadratic model of fractionation sensitivity [37]. In this empiric model, "late-reacting" normal tissues such as fibroblasts and neurons have a low α/β ratio (2-5 Gy) and are very responsive to increases in fraction size, while "acutely-reacting" normal tissues such as intestinal epithelium have a high α/β ratio (>7 Gy) and are less responsive to changes in fraction size. The biological effect of a given fractionation scheme size is related to the α/β ratio by the equation:

Effect = E = n(αd + βd2) where

d = dose/fraction

n = # of fractions

Although relatively high cumulative doses of radiation are needed for tumor control, the daily fraction size has to be respectful of the fraction sensitivity of normal tissues in the treated volume. Accounting for these assumptions, increases in fraction size have to be compensated for by reductions in cumulative radiation dose, which typically are insufficient for tumor control. As a result, daily fractions of 1.8 to 2 Gy are delivered over 4-6 weeks to reach a cumulative dose of 45-60 Gy. In vitro experiments in human breast carcinoma cell lines have suggested an α/β ratio of about 4 Gy [38, 39]. In 1986 Royal Marsden Hospital and the Gloucestershire Oncology Centre collaborated in a prospective trial evaluating 3 breast fractionations. [1, 40]

50 Gy in 25 fractions over 5 weeks

39 Gy in 13 fractions (3.0 Gy/fx) over 5 weeks

42.9 Gy in 13 fractions (3.3 Gy/fx) over 5 weeks.

In 1999, after over 1400 patients had been enrolled, the trial design was expanded into a multi-institutional trial and patient data from the earlier study was rolled into what became Start A, with the 13 fraction regimen changed to 3.2Gy/day for 41.6Gy [5]. A total of 2236 women were randomized to one of three arms between 1986 and 1999:

The overall treatment time was kept constant in all three arms. The primary endpoint was late breast change. Local control was a secondary endpoint. The protocol did allow treatment of regional lymph nodes (supraclavicular and axillary) with additional radiation fields, and these were used in 20% of the patients. Fourteen percent of patients received CMF chemotherapy. It must be noted that none of the 290 patients who were treated to the axilla and supraclavicular areas developed brachial plexopathy in the initial publication. At 10 years, however, there was one reported case of plexopathy in the high dose 41.6Gy arm. A major limitation of the study is the use of a conventionally fractionated boost of 14 Gy in 7 fractions. How this boost interacted with the altered fractionation effects is unclear. It also unfavorably impacts the convenience of the experimental arms.

Running in parallel to Start A, Start B was an accelerated hypofractionation trial comparing 50Gy in 2Gy daily fractions for 5 weeks versus 40Gy delivered in 2.67Gy daily for 15 days. Results were described above. These trials are both limited in their applicability as only small proportion of patient were treated post mastectomy and with regional nodes radiated, in addition to the fact that chemotherapy was mostly CMF based and radiation centers were allowed to use 2D planning and lower energy cobalt.

Again in the setting of an intact breast, NCI Canada randomized 1234 patients (1993-1996) with T1 and T2 tumors with negative margins and pathologically negative nodes (on level 1 and 2 dissection) to:

1. 50 Gy in 25 fractions (2 Gy/fx) over 35 days or
2. 42.5 Gy in 16 fractions (2.66 Gy/fx) over 22 days [41].

Dose was prescribed to the 1/3rd point, and homogeneity within 7% was required. Lumpectomy bed boost and treatment to regional draining lymph nodes was not allowed. With a median follow-up of 9.3

years, there was no difference in local regional recurrence, OS and DFS. Cosmesis was identical with excellent or good scores at 3 and 5 years in 77% of patients in both groups. Toxicities were comparable. Grade 2 and 3 toxicities were negligible. At 5 years, 87% of women in the experimental arm had no skin toxicity, and 66% of women had no subcutaneous toxicity, compared with 82% and 60% in the control arm, respectively. A major limitation of the Canadian study is the lack of a lumpectomy boost, which has been shown in prospective randomized trials to significantly improve local control [42, 43]. The patients eligible for the study had low risk for disease recurrence, limiting the general scope of the results. In addition, the regional nodes were untreated, making the safety of irradiating a larger volume unclear.

Rodger, et al. at the Western General Hospital, Edinburgh, UK, published a retrospective review of late effects in post-mastectomy patients before and after a policy change in their department, changing from 4.5 Gy times 10 fractions over 4 weeks to 2.25 Gy times 20 fractions, after a simple mastectomy. All patients were treated to the regional lymph nodes, and dose to supraclavicular and axillary areas was 4.25 Gy times 10 in the hypofractionation arm. 484 patients were treated with the 10 fraction regimen during 1/1979 and 3/1982, while 289 patients were treated with the 20 fraction regimen from 4/1982-12/1984. There were more late effects in the hypofractionation arm: Grade 3-4 skin effects on the chest wall 29/79 (37% vs. 0 (0/92)), subcutaneous effects 66% vs. 10% on the chest wall and 29% vs. 14% in the axilla. Grade 2-3 arm edema was also higher 29% vs. 14%, as were rib fractures 52% vs. 11%. Two plexopathies were seen in each group. The two regimens produced equal disease control. Although not a randomized comparison, the outcomes reported in this study are instructional, especially in light of the linear-quadratic model, which was not available to the clinicians in Edinburgh. Assuming an α/β ratio of 4 Gy, the patients received a whole breast dose equal to 58 Gy in 2 Gy fractions, (Gy4=87.65, while 50 Gy in 2 Gy=75 Gy4). It would appear from this analysis that the patients were over treated.

This 16 day radiation treatment design is supported in its safety and efficacy through randomized trials in early stage breast conservation, and will reduce cost while likely improving patient satisfaction for women requiring PMRT. The promise of short-course PMRT lies in the added convenience it may offer to patients who otherwise may not be able to receive PMRT, and it may also allow earlier sequencing of PMRT with systemic chemotherapy. Although sequencing seems to be unimportant in the context of breast preservation [44], it may be important in women at higher risk for locoregional recurrence. In the trial, we will allow adjuvant chemotherapy to be delivered before or after PMRT. Given the excellent cure rates and low morbidity with current adjuvant radiation therapy technique and fractionation, it is only natural that subsequent improvements in the field take convenience and economic impact into account.

1.4 Patient Satisfaction and Well-being as Patient Reported Outcomes (PROs)

The assessment of patient-reported outcomes (PROs) in clinical research provides important insight into how therapies impact the daily lives of patients. There is a growing recognition that patient-reported endpoints are critical in oncology trials, particularly when cosmesis and toxicity are likely to be different in the treatment arms. Patient-reported adverse event collection has been shown to be more thorough than collection by provider-report, with consistent underreporting of side effects by providers.[69] Patient-reporting of health-related quality of life has become the gold standard in part because providers have been found to underestimate the pain and distress their patients are experiencing. [70-72]

In a trial of different radiation schedules, in which cosmesis may be substantially different in the two arms of the study, patient-reported satisfaction and well-being are particularly important. Although short-term differences between the treatment arms may be momentarily relevant to patients, the long-term cosmetic outcomes are most critical, so we have chosen to collect these data at 24 months (and compare to pre-treatment measures). In order to avoid burdening patients, we will not survey them for satisfaction or well-being in between these time points.

1.4.1 Lymphedema Background

Patient-reported outcomes such as symptom assessment and QOL can serve multiple purposes, including acting as validation measures of treatment efficacy in the context of clinical trials and serving as reference points for clinical decision-making when modest differences in survival are anticipated among various treatment modalities [48-50]. It is possible in this trial that while the treatment outcomes with respect to disease recurrence are equivalent that the morbidity associated with each of the treatment arms is not the same. In this setting, it is critical that a comprehensive assessment of treatment-associated morbidity be performed in order to represent the entirety of the treatment experience. As the contemporary treatment for breast cancer evolves, it is important to examine the morbidity associated with various treatment regimens.

Arm Lymphedema: Arm lymphedema is one of the most dreaded complications of breast cancer treatments, in that it often causes physical discomfort, psychological distress, functional impairment, change in body habitus and self-image, chronic disability, and diminished QOL [51-55]. In addition, lymphedema incurs significant financial costs, both to the affected individual and to the national and international health care delivery systems. In a review of the published literature concerning breast cancer treatment-related lymphedema, Erikson et al. concluded "there is need for better understanding of the prevalence and morbidity of arm edema in population-based studies" [56]. As the contemporary treatment for breast cancer evolves, it is particularly important to examine the incidence of lymphedema and associated symptoms.

Of those treated for breast cancer, it has been reported that the incidence of lymphedema varies widely depending on the criteria applied [57]. The most common estimates reported are 20 to 40% for women undergoing axillary lymph node dissection [58-63]. The challenges related to lymphedema measurement, diagnosis, and follow-up are cited as the primary reasons for these large discrepancies in reported lymphedema incidence.

Armer et al. have reported that in a cohort of 211 breast cancer participants with 30 months post-treatment follow-up who were assessed using perometry, circumferences, and symptom assessment that the incidence of lymphedema ranged from 41 to 91% with 2 cm being the highest estimation method and symptoms the lowest [57, 64].

In a recent report from the NSABP B-32 trial, arm volumes were assessed over 3 years following axillary lymph node dissection (n=1,975) or sentinel lymph node biopsy (n=2,006) using water displacement techniques. In this study, arm volume differences were only noted for 14% (compared to 8.6% at baseline) of patients undergoing axillary lymph node dissection and 7.5% (compared to 8.0% at baseline) of those undergoing sentinel lymph node biopsy. [65] Numbness and tingling were the two symptoms assessed in this study, as well as shoulder abduction. Radiation to the axilla was reported to increase the risk for residual arm volume difference (OR = 3.47) however the actual number of patients treated with XRT was very small (ALND Group: n = 22, 1.1% and SLND Group: n=13, 0.7%). While the reported incidence of lymphedema following sentinel node biopsy concurs with other studies, the reported incidence of limb volume differences following axillary dissection was lower than that reported in the majority of studies. Although this study provides some paired symptom data with objective measures of lymphedema, key symptoms of lymphedema (i.e. heaviness and swelling) were not included, and the very small number of patients treated with XRT demonstrates the gap in knowledge that we propose to address in the current trial.

Whether or not radiation treatment to the axillary lymph nodes or breast/chest wall increases the risk of developing lymphedema and/or associated symptoms is still unresolved. A number of studies have reported that there is no association. [60, 66]

It is even more unclear whether or not axillary XRT alone (or following sentinel lymph node biopsy) increases the risk of lymphedema. Therefore, in the setting of this proposed breast cancer treatment trial, it is imperative to obtain objective clinical assessment data and to use validated lymphedema symptom assessment tools to inform future decision-making related to these cancer

therapies. The clinical and patient-reported lymphedema assessments are more thoroughly described in Section 10.5.

1.4.2 Breast Q Survey

We will be using the Breast Q survey tool to assess patient satisfaction and well-being. [81-83] This tool has been validated for use in patients before and after mastectomy with reconstruction to assess well-being and patient satisfaction with results, and is provided free of charge for academic research. Cronbach's alphas for the scale range from 0.81 to 0.98, and the BREAST-Q has test-retest reliability, demonstrated by an intraclass correlation coefficient ranging from 0.85 to 0.987.[73]

1.4.3 Was it Worth It Questionnaire

The Was It Worth It instrument was developed to learn more about the experience of patients participating in clinical trials. It is comprised of four brief questions, and it has also been called the "Trial Satisfaction" survey.[74] Although formal validity and reliability data for this instrument are not yet available, multiple cooperative group studies have used it to measure how satisfied patients end up with their decision to enroll on a clinical trial.[75-79]

1.5 Photographic Cosmetic Assessment

There are no validated photographic assessment tools in patients with breast reconstruction. The EORTC Breast Cosmetic Rating system is a digital photographic method that has been utilized in prior radiation studies and shown to be reliable and valid in detecting effects of radiation morbidity. [45-47] This method compares the radiated breast with the contralateral untreated side and evaluates: Size, shape, location of the areola/nipple, appearance of the surgical scar, skin pigmentation changes, presence of telangiectasia and a global cosmetic score based on all of the factors. Characteristics are graded on a four-point scale: 0, excellent or no difference; 1, good or small difference; 2, fair or moderate difference; and 3, poor or large difference.

1.6 Study Hypotheses

- Short course hypofractionated radiation has a non-inferior reconstruction complication rate compared to standard fractionated radiation.
- Short course hypofractionated radiation offers reconstructed women better cosmesis, reduced lymphedema, and quality of life with a similar rate of cancer recurrence and treatment toxicity.

2.0 OBJECTIVES

2.1 Primary Objective

To evaluate whether the reconstruction complication rate at 24 months post radiation is non-inferior with hypofractionation. Complications will include those listed in Section 10.1.

2.2 Secondary Objectives

2.2.1 To evaluate the incidence of acute and late radiation complications based on CTCAE 4.0 toxicity.

2.2.2 To evaluate the local and local regional recurrence rate.

2.2.3 To compare reconstruction complication rates based on reconstruction method (autologous +/- implant vs implant only) and timing of reconstruction received (immediate vs. intent for delayed).

2.3 Photographic Cosmetic Assessment

2.3.1 To evaluate reconstructed breast photographic cosmetic scores with hypofractionated radiation compared to standard fractionation 24 months after radiation.

2.3.2 To evaluate reconstructed breast photographic cosmetic scores 24 months after radiation based on the method and timing of reconstruction received.

2.4 Lymphedema Assessment

2.4.1 To estimate the incidence of arm lymphedema by treatment arm.

2.5 Patient Reported Outcomes (PRO) Objectives

2.5.1 To compare physical well-being, psychosocial well-being, sexual well-being, satisfaction with breast/nipples/abdomen, and satisfaction with overall outcome between the treatment arms at 24 months after radiation.

2.5.2 To estimate patient satisfaction with trial participation by treatment arm as measured by the Was It Worth It Questionnaire at 24 months after radiation.

2.6 Economic Analysis

2.6.1 To compare the direct and indirect patient costs for radiation therapy by treatment arm.

2.6.2 To compare patient reported total health care service utilization 12 months after the completion of radiation.

2.6.3 To compare the economic impact of treatment.

2.7 Correlative Science Objectives

2.7.1 To analyze polymorphisms in MDM2 and in genes including TP53, ATM, TGFB1, IL4, IL6, and IL10 and determine correlations with a higher likelihood of adverse radiation reactions (radiation sensitivity) and with toxicities

2.7.2 To analyze polymorphisms in MDM2 and in genes including TP53, ATM, TGFB1, IL4, IL6, and IL10 to determine correlations with secondary endpoints such as local-regional control.

3.0 PATIENT SELECTION

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

3.1 On-Study Guidelines

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

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

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Women of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).
- Medical conditions, genetic mutations or active medications that might make the patient more susceptible to radiation toxicity.

3.2 Eligibility Criteria

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

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

_____ **3.2.1 Histologically confirmed invasive carcinoma of the breast** of any of the following histologies (ductal, lobular, mammary, medullary, or tubular). Patients with metaplastic breast cancer are not eligible.

_____ **3.2.2 Patients will be staged according to the TNM staging system.**

For patients *not* receiving neoadjuvant chemotherapy, pathologic staging must be T0N1-2a, T1N1-2a, T2N1-2a, T3N0-2a, and all M0 status.

For patients receiving neoadjuvant chemotherapy, clinical pre-chemo staging and post mastectomy pathological staging is required for all patients. Patients who have received neoadjuvant chemotherapy and are pathologically cT0-2 and N0 are only eligible if biopsy-proven clinically N1 or N2 disease is documented prior to the start of neoadjuvant chemotherapy. cT3N0 patients or ypT3N0 patients who receive neoadjuvant chemotherapy may be eligible based on clinical or pathological T stage, and do not require pathologically positive lymph nodes.

Note: Higher of the clinical or pathological T and N stage are used for final staging, if receiving neoadjuvant chemotherapy.

All patients with clinical, radiographic or pathological T4, N3 or involved internal mammary disease (N1b, N1c, and N2b) are not eligible. **N1mic patients are eligible.**

_____ **3.2.3 No prior therapeutic radiation therapy to the chest, neck or axilla. Prior radioactive oral iodine is permitted.**

_____ **3.2.4 No prior history of ipsilateral breast cancer (invasive disease or DCIS)**. LCIS and benign breast disease is allowed.

_____ **3.2.5 No history of prior or concurrent contralateral invasive breast cancer.** Benign breast disease, LCIS or DCIS of contralateral breast is allowed.

_____ **3.2.6 No active collagen vascular diseases**, such as: systemic lupus erythematous, scleroderma, or dermatomyositis.

_____ **3.2.7 Negative inked histologic margins from mastectomy pathology** (no invasive cells at margin). **Patients with DCIS at margin are eligible.**

_____ **3.2.8 No significant post mastectomy complications in the ipsilateral or contralateral breast requiring an unplanned re-operation or admission for IV antibiotics.** Re-operation for margins evaluation, nodal completion and routine reconstruction is acceptable.

_____ **3.2.9 Radiation oncologist intends to treat all target volumes described in section 7.4 and respect all normal tissues identified in section 7.4.3 in accordance with the dosimetric constraints described** (simulation before registration recommended)**.**

_____ **3.2.10 Radiation oncologist is planning to treat regional lymph nodes including internal mammary nodes and meet acceptable protocol dosimetric requirements.**

_____ **3.2.11 Radiation oncologist is NOT planning to utilize a chest wall/scar boost.**

_____ **3.2.12 Patient must have undergone immediate reconstruction at the time of mastectomy or be planning to undergo reconstruction within 18 months after radiation.**

_____ **3.2.13 Treating physician and patient must plan to start radiation treatment within the timeframes specified in Section 7.0.**

____ **3.2.14 If a tissue expander is utilized it needs to be a fluid filled expander, NO air expander (unless completely deflated) during radiation therapy.**

_____ **3.2.15 For patients with diabetes, hemoglobin A1C test must have been performed ≤ 90 days prior to registration.**

_____ **3.2.16 No co-existing medical conditions with life expectancy < 5 years.**

_____ **3.2.17 No other malignancy within 5 years of registration** with the exception of basal cell or squamous cell carcinoma of the skin treated with local resection only or carcinoma in situ of the cervix.

_____ **3.2.18 Negative pregnancy test (serum or urine HCG) in women of child-bearing potential ≤ 7 days prior to registration.** Patients who have received a bilateral tubal ligation still require a negative pregnancy test for eligibility.

A female of childbearing potential is a sexually mature female who has not undergone a hysterectomy or bilateral oophorectomy and has not been naturally postmenopausal for at least 12 consecutive months.

_____ **3.2.19 Women of child-bearing potential must agree to utilize a form of birth control or agree to undergo sexual abstinence during radiation therapy.**

_____ **3.2.20 ECOG (Zubrod) Performance Status 0-1**

_____ **3.2.21 Patient ≥ 18 years of age**

_____ **3.2.22 Patients must be able to read and comprehend English, in order to be able to complete study questionnaires.** However, patients participating through CCTG institutions who can read and comprehend French are eligible.

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate registration with CTEP

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

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

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

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

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

4.2 CTSU Site Registration Procedures

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

IRB Approval:

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

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

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

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

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

4.2.1 Additional site registration requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.2 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website [redacted] using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number [*A221505*].

• Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.3 Protocol Specific requirements for A221505 Site Registration

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

4.2.4 Submitting Regulatory Requirements

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

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

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

4.2.5 Checking Your Site's Registration Status

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

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

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

4.2.6 Credentialing

See Section 14.0 for credentialing requirements.

4.3 Patient Registration Requirements

All patients must have completed mastectomy prior to registration, and must be registered prior to initiation of radiation therapy.

- **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 questionnaire booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A221505 CTSU site) and submitting the form through the CTSU regulatory portal. Samples of the assessments are found in Appendices II-V, which are to be used for reference and IRB submission only. They are not to be used for patient completion.

4.4 Patient Registration/Randomization Procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for

retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

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

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

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

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

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

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

4.5 Registration to Correlative and Companion Studies

There is one substudy within Alliance A221505. This correlative science study **must be** offered to all patients enrolled on Alliance A221505 (although patients may opt to not participate). This substudy does not require separate IRB approval. The substudy included within Alliance A221505 is:

- Biological correlates of adverse radiation response in A221505, Alliance A221505-ST1 (Section 13.1)

If a patient answers "yes" to "My samples and related information may be used for the additional study described above," Question #1 in the model consent, they have consented to participate in the substudy described in Section 13.1. The patient should be registered to Alliance A221505-ST1 at the same time they are registered to the treatment trial (A221505). Samples should be submitted per Section 6.2.

4.6 Stratification Factors and Treatment Assignments

The factors listed below will be used as stratification factors. After a patient has been registered, the values of the stratification factors will be recorded, and the patient will be assigned to either hypofractionated or standard radiation dosing using the Pocock and Simon dynamic allocation

procedure, which balances the marginal distributions of the stratification factors between the treatment groups (Pocock-Simon).

Patients will be stratified before randomization based on planned intent for:

- autologous (+/- implant) vs.
- implant only breast reconstruction.

• Patients will be stratified before randomization based on:

- immediate reconstruction vs.
- planned for delayed breast reconstruction (**includes patients who have had no reconstruction or only a temporary expander placed at time of randomization**.)

** Patients undergoing immediate reconstruction will already have completed reconstruction at the time of randomization.

*** Patients who have a tissue expander placed at the time of mastectomy and then have a delayed final reconstruction will be classified as delayed for purposes of stratification and randomization.

5.0 STUDY CALENDAR

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

Pre-Study Testing Intervals

- To be completed ≤ 7 DAYS before registration: Pregnancy test,
- To be completed ≤ 28 DAYS before registration: history and physical.

	Prior to Registration	Before RT¥	At completion of RT€	2 to 8 weeks post RT	6, 12, 18 mos. post RT*	2 years post RT*	30 mos., 3,4 and 5 years post RT**	10 and 15 years post RT***
Tests & Observations								
H&P, Weight, PS	X	X (1)	X	X	X	X	X	
Height	X							
Mastectomy or reconstruction complications		X	X	X	X	X	X	
Recurrence (scan or clinical) Assessment					X	X	X	X
Adverse Events Assessment		A	A	A	A	A	A	
Clinical Lymphedema Assessment		B	B	B	B	B	B	
Cardiac and Brachial Plexopathy Events					C	C	C	C
Arm Circum. Measure (see §10.5)		X			X (2)	X		
Photographs for Cosmetic Assessment		D				X (4)		
Laboratory Studies								
Serum or Urine HCG	E							
Hemoglobin A1C	F							
Questionnaires								
Breast-Q Post-mastectomy		G						
Breast-Q Post-reconstruction		G				X	X (3)	
LBCQ		X			X (2)	X	X (3)	
BLE		H			X (2)	X	X (3)	
Economic Surveys		I	J	I	J			
EQ-5D-3L		X			X	X		
Was It Worth It Questionnaire						X		
Correlative Study (optional) Whole Blood	*To be collected at baseline, see Sections 6.2 and 13.1*							

¥ May be completed at any time following patient consent (before or after registration, but prior to treatment)
€ May be completed within 72 hours of last radiation treatment.
* +/- 6 weeks.
** For 30-month visit, +/- 6 weeks; for 3, 4, and 5-year visits, +/- 3 months
*** +/- 6 months. All follow up, including survival status, done after 5 years will be gathered by record review only.
A Assessment of side effects related to radiation therapy should be assessed according to the history and physical examination.
B To be assessed per the CTCAE criteria.
C Will be assessed by medical record review.
D Only for patients with final reconstruction completed before radiation.
E For women of childbearing potential. Must be done within 7 days prior to registration.
F For diabetic patients only, to be done ≤ 90 days before registration.
G Breast Q Post Mastectomy questionnaire; unless already reconstructed, then Breast-Q Post Reconstruction.
H Only for patients who have had reconstruction
I Prior to RT, patients will be given the Patient Health Care Diary and the Health Care Expense Questionnaire (Appendix VII) to be returned to the clinic at the 2 to 8 week visit (see Section 10.7).
J After completion of RT, the patient will be given the Patient Health Care Utilization Diary (Appendix VIII) and will be asked to return it at the 12–month visit (see Section 10.7).
1 Need not be repeated if done within the past 30 days
2 To be completed at 6 months only. (up to 18 months, whenever reconstruction is completed, for BLE)
3 To be completed at 5 years only.
4 +/- 2 months

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule:

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

6.1.2 Medidata Rave

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

Requirementsto access Rave via iMedidata:

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

Rave role requirements:

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

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

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login [redacted] using their CTEP-IAM username and password, and click on the accept link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

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

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.4). Samples of questionnaire booklets are available in Appendices I-III for reference and IRB submission only. They are not to be used for patient completion. Booklets

must be given to patients to complete and patients should be instructed to return the booklets to site staff either in person or by mail and site staff will enter patient and caregiver responses into Rave.

The patient questionnaires for this study are only being made available in English for US participants.

CCTG institutions are to provide patient completed booklets translated into French to French speakers. The site is responsible for transcribing the patient responses from the French version into the English version, within Medidata Rave to submit to the Alliance Statistics and Data Center. The institution should retain the completed French version as source documentation.

6.1.3 Data Quality Portal:

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

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

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

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

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

6.1.4 Supporting Documentation

This study requires supporting documentation for pathology from mastectomy, clinical staging document at baseline, all operative notes, and any notes documenting complications or progression.

CPT Chart summary: To be completed at 12 months only. Summary of CPT billing codes from treating institutions in the U.S. from registration until 12 months after radiation.

6.2 Specimen collection and submission

All participating institutions must ask patients for their consent to participate in the correlative substudy planned for Alliance A221505-ST1, although patient participation is optional. Pharmacogenetic studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.0. For patients who consent to participate whole blood will be collected at the following time point for this study:

	Following registration and prior to RT*	Storage/ Shipping conditions	Submit to:
Whole blood (EDTA/lavender top) (see Section 6.2.2)	10 mL	pack/ship on cold pack over night	Alliance Biorepository at Mayo Clinic BAP

* Can be collected at any time, sites can schedule this blood draw to coincide with a standard of care blood draw

6.2.1 Specimen submission using the Alliance Biospecimen Management System

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 (Safari, Firefox, Internet Explorer). 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 contact: [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 submitted specimens must be labeled with the protocol number (A221505-ST1), Alliance patient number, patient's initials and date and type of specimen collected (e.g., serum, whole blood).

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Ship specimens on Monday through Friday only. Shipping by overnight service to assure receipt is encouraged. Do not ship specimens on Saturdays or the day before a holiday.

All specimens should be sent to the following address:

[redacted]

6.2.2 Whole blood collection, processing, and shipment

Whole blood collection: For patients who consent to participate, whole blood samples will be collected for the biomarker analyses described in Section 13.1.

Collect 10 mL of peripheral venous blood in one or two lavender top tubes (K2EDTA anti-coagulant) at baseline (following registration and prior to radiation therapy).

Whole blood processing: The tube(s) should be inverted several times to mix the EDTA and refrigerated until shipped on cool pack by overnight mail to the Alliance Biorepository.

Label EDTA tubes with the following information:

1) Alliance study number (i.e., A221505)
2) Alliance patient number
3) Patient's initials (last, first, middle)
4) Procurement date and time
5) Whole blood

Shipping: The samples should be shipped the same day that the blood is drawn per Section 6.2.1.

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

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

6.3.1 TRIAD Access Requirements

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

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

6.3.2 TRIAD Installations

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

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

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

6.3.3 Procedures for Data Submission via TRIAD

Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan and dose files. This study uses TRIAD for RT data submission. Use of TRIAD requires several preliminary steps as described above. See Section 4.2 for details. Additional information is available at: [redacted]

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

See Section 7.5 for items to be submitted for RT QA on-treatment review.

6.4 Submission of Photographs for Cosmetic Assessment

Photographs of both breast/reconstructed chest walls at the following time points will be submitted to IROC Rhode Island:

- Before radiation, only for patients with immediate reconstruction (only for those patients whose reconstruction is complete with final implants)
- 24 months after the completion of radiation for all patients

The photographs should be in an image format such as .jpg. Scanned photographs will not be accepted.

See section 10.6 for instructions on taking the photograph.

The de-identified photographs should be submitted via email to [redacted] Please put the protocol number and patient's study ID in the subject line of the email. Alternatively, photographs can be uploaded via TRIAD or submitted via sFTP. See 6.3.3 for instructions for submission via sFTP.

Questions regarding documentation should be directed to: [redacted]

7.0 TREATMENT PLAN/INTERVENTION

Radiation treatment may begin no sooner than 21 days after initial surgery or 21 days after the completion of adjuvant chemotherapy. Radiation therapy must begin no later than 84 days (12 weeks) after initial surgery or the completion of adjuvant chemotherapy, whichever is later.

- **Initial surgery** is defined as mastectomy and any subsequent surgeries related to the initial mastectomy, including additional margin resection, lymph node removal or immediate reconstruction. If neoadjuvant chemotherapy is used, then surgery must occur within 56 days after completing the cytotoxic component of therapy.
- **Chemotherapy** is defined as cytotoxic chemotherapy, not biological therapy, such as trastuzumab, pertuzumab, etc. Trastuzumab emtansine (Kadcyla) is classified as biological therapy for the purposes of this protocol and NOT chemotherapy.

Randomization: Patients will be randomized to either radiation in 25 fractions over 5-6 weeks or hypofractionation radiation in 16 fractions over 3-4 weeks. Radiation will be delivered to the chest wall/reconstructed breast and regional lymph nodes. The treating radiation oncologist must certify intent to treat regional lymphatics prior to registration.

7.1 Surgical Management

7.1.1 Mastectomy

Surgery may be completed as a total, simple, skin sparing, nipple sparing or modified radical mastectomy.

Margins should be negative, defined as no tumor on ink. A focally positive deep margin will be considered a negative margin if the deep margin is the pectoralis fascia and the pectoralis fascia was noted as removed in the operative description or pathology report. This is provided there is no evidence of pectoralis fascia invasion by imaging or pathological evaluation.

Lymph nodes must be evaluated by sentinel node biopsy or axillary dissection. The majority of these patients will have positive lymph nodes in order to qualify for enrollment. This protocol does not stipulate sentinel node versus axillary dissection, but does require lymph node management per standard of care. Patients will be recorded as having undergone a sentinel node only procedure or an axillary dissection. A sentinel node procedure will be considered an axillary dissection if more than 5 lymph nodes are removed.

Mastectomy and nodal evaluation must be completed within 56 days of the completion of neoadjuvant chemotherapy. Radiation must start per section 7.0.

7.1.2 Surgical Quality Assurance Requirements

There is no surgical credentialing required for participation in this trial. There is also no surgical quality assurance required for this trial.

Negative margins should be achieved prior to proceeding on to adjuvant radiation therapy. Negative margins are defined in section 7.1.1.

7.2 Breast Reconstruction

Reconstruction of the breast may occur before or after radiation but must be completed within 18 months of finishing radiation therapy, unless medically contraindicated.

A fluid filled tissue expander may be placed before or after radiation and maybe inflated or deflated for radiation. No change in volume of the expander may occur after radiation simulation and before the last fraction of PMRT. Air tissue expanders are not recommended and if utilized, must be deflated for radiation simulation and treatment delivery due to the difficulty with dose calculation and reporting at air/tissue interfaces. Additionally, the tissue expander is part of the radiation target volume, which must receive the prescription dose which is not possible in air.

Plastic surgeon may use any combination of allograft, saline, silicone, or autologous tissue flap for reconstruction. The method and timing of reconstruction must be documented on the eCRF.

Reconstruction intent must be stated at the time of registration, and may include the following:

- Implant only reconstruction before radiation
- Autologous reconstruction before radiation (with or without implant)
- Temporary expander placement at the time of mastectomy, radiation, with subsequent delayed reconstruction with implant only
- Temporary expander placement at the time of mastectomy, radiation, with subsequent delayed reconstruction with autologous tissue with or without implant
- Mastectomy without tissue expander, followed by radiation, with subsequent delayed reconstruction with implant, only.
- Mastectomy without tissue expander, followed by radiation with subsequent delayed reconstruction with autologous tissue with or without implant

7.3 Systemic Therapy

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

Chemotherapy is allowed. If adjuvant chemotherapy is indicated, it can be delivered before or after radiation therapy. Neoadjuvant chemotherapy is allowed. Patients may be co-enrolled on systemic therapy trials, if there is no contraindication on the other trial.

Cytotoxic systemic therapy may not be used concurrently with radiation, however, trastuzumab, pertuzumab or other biological therapy may be given concurrently per standard of care. Trastuzumab emtansine (or Kadcyla) will be considered a biological therapy and can therefore be given concurrently with radiation treatment.

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

7.4 Radiotherapy

All radiation therapy questions should be directed to the Alliance A221505 Radiation Co-Chairs.

The radiation methods and dose volume parameters are adapted from RTOG criteria, as outlined in the RTOG breast atlas: [redacted]

Radiation therapy treatment planning should begin after consultation with the radiation oncologist and prior to radiation treatment.

A deviation unacceptable will be scored for failure to prescribe proper dose and not treating the required regional lymph nodes, including IMs.

The use of a radiation chest wall or scar boost is not allowed on this trial. If the radiation oncologist feels that a particular patient must receive a scar boost, she should not be enrolled on this trial. Use of a scar boost on an enrolled patient will be scored as a deviation unacceptable, but these patients will still be followed.

Every attempt should be made to meet dose constraints. If dose constraints are not met, patients will remain on protocol treatment unless in unusual circumstances it is recommended that they be removed from protocol treatment by a radiation co-chair. It is recommended this be discussed with a radiation co-chair prior to starting radiation.

Patients will be registered after mastectomy and randomized to one of the following study treatment arms:

Arm 1: Conventional fractionation radiation to the chest wall or reconstructed breast, supraclavicular fossa, axilla and internal mammary nodal basin. 50 Gy in 25 daily 2 Gy fractions. Treatment will be given 5 days a week for 5-6 weeks (no treatment weekends and holidays).

Arm 2: Hypofractionated radiation to the chest wall or reconstructed breast, supraclavicular fossa, axilla and internal mammary nodal basin. 42.56 Gy in 16 daily 2.66 Gy fractions. Treatment will be given 5 days a week for 3-4 weeks (no treatment weekends and holidays).

In the case of a departmental holiday, RT may be given 4 days a week. In case of medical illness or RT side effect(s), treatment breaks are allowed as needed per standard practice.

For both randomized treatment arms, radiation is to be delivered to the following planning target volumes: the reconstructed breast/chest wall, undissected axilla*, supraclavicular fossa and internal mammary nodal chain in the first 3 intercostal spaces.

* The undissected axilla typically includes the high level II and Level III nodes. If an axillary dissection has been performed, RT will only be directed to the un-dissected axilla.

The use of **skin bolus** is often utilized with post-mastectomy irradiation, but ultimately is per the treating physician's discretion to individualize to the patient's treatment and radiotherapy plan. If using bolus, the skin dose should follow the same constraints as the Chest wall PTV Eval.

7.4.1 Technical Factors

3-dimentional CT based treatment planning is required. Megavoltage photon beam energies with energies ≥ 4 MV are required. Electron beams require megavoltage energies, if utilized. Proton beams are not allowed on this trial.

Localization, simulation and immobilization

Simulation and treatment must be performed with the patient in the supine position. Patients should be optimally positioned with alpha cradle casts, vac fix, breast boards, wing boards and/or other methods of immobilization at the discretion of the treating physician.

Methods to minimize the cardiac exposure to RT such as a heart block, gating or breath-hold are allowed at the discretion of the treating physician.

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

The treatment planning CT must be post-mastectomy.

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

For patients who have a fluid filled expander placed at the time of mastectomy, the amount of fluid in place at the start of radiation is per the treating physician's discretion. The position of the

expander, ranging from collapsed to fully expanded, that is present at the time of acquisition of the CT scan for treatment planning, must remain stable until the completion of radiotherapy. In the setting of a contralateral mastectomy with expander placement, contralateral expansion should not increase contralateral chest wall/reconstructed breast exposure to radiation. In this situation, it is recommended to at least partially deflate the contralateral expander before RT simulation. Per Section 3.2 and Section 7.2, air expanders are not recommended and if utilized should be fully deflated during planning and treatment due to dosimetric reporting difficulties, as the expander is part of the chest wall CTV and PTV.

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

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

Use of IMRT is allowed if credentialed. Please see the section below for IMRT guidelines.

Calculations shall take into account the effect of tissue heterogeneities.

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

Post Mastectomy Volumes: Mastectomy Scar, Chest wall, levels I, II, III axilla, supraclavicular, and internal mammary nodes in the first 3 intercostal spaces as defined in the RTOG Breast Atlas and below.

Normal tissue: Right and left lung, contralateral breast, heart, thyroid.

Normal tissues should be delineated as follows:

Contralateral breast: Includes the apparent CT glandular breast tissue visualized by CT and consensus definitions of anatomical borders from the RTOG Breast Atlas. In the setting of a contralateral mastectomy, there will instead be a contralateral chest wall or contralateral reconstructed breast instead of a contralateral breast. In general the borders are:

- *Posterior border*: At the anterior surface of the pectoralis, serratus anterior muscles excluding chest wall, ribs, boney thorax, and lung/heart.
- *Medial border*: The sternal-costal junction.
- *Lateral border*: Varies based on the size of the breast, but typically is at the mid-axillary line and excludes the ipsilateral lattismus dorsi muscle.
- *Cephalad border*: Should be similar to that of the ipsilateral breast CTV.
- *Anterior border:* Skin minus 5 mm to minimize inaccuracy of dose calculation at the skin surface.

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

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

Thyroid: The thyroid is easily visible on a non-contrast CT due to its preferential absorption of iodine, rendering it "brighter" or denser than the surrounding neck soft tissues. The left and right

lobes of the thyroid are somewhat triangular in shape and often do not converge anteriorly at mid-line. All "bright" thyroid tissue should be contoured. For patients who have undergone total thyroidectomy, there may be no thyroid tissue to contour.

IMRT

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

1) The treatment plan will be considered IMRT for the purposes of this protocol if an inverse planned optimization is used to determine the beam weights to meet the target and critical structure dose-volume constraints.
2) A plan generated by direct aperture optimization that employs an inverse planning algorithm is considered as IMRT when the target and critical structure dose-volume constraints are met and at least 3 apertures for each beam direction are used.
3) If IMRT is combined with the standard open medial and lateral tangential fields for whole breast irradiation, the IMRT beam, as described in number 1) above, should deliver > 50% of the total number of monitor units for the beam orientation.
4) If an IMRT plan is used with another IMRT plan, forward-planning photon beams, and/or electron beam, the composite dose distribution and DVHs should be generated.
5) All standard IMRT planning and delivery systems using MLC (step-and-shoot, dynamic MLC, slide-and shoot, VMAT, tomotherapy) are allowed and classified as IMRT as long as target and critical structure dose-volume constraints are met.
6) IMRT planning and delivery systems using physical beam-intensity compensators designed by an inverse algorithm to modulate beam intensity so that the required dose constraints are met are also accepted as IMRT.
7) The patient specific pre-treatment QA measurement is required prior to the first treatment for an IMRT plan.

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

- The plans generated using forward-planning methods or segmental techniques such as "field-in-field" to meet dose-volume constraints are considered as 3DCRT plans. These forward-planned or segmental treatment techniques are those intended mainly to improve the uniformity of the dose distribution, but not to produce steep dose gradients to protect critical structures (e.g. heart or lung).
- The plans with the number of apertures < 3 for each beam direction are considered 3DCRT plans even if they were generated with inverse planning algorithms.

7.4.2 Treatment Planning

The goals of treatment planning in this study in both arms are to encompass the chest wall or breast and nodal PTVs and minimize inclusion of the heart and lung.

Field arrangements for 3D conformal and IMRT of the chest wall/breast and nodal PTVs are defined below with some discretion of the treating physician. Multiple beam arrangements are to be designed during the treatment planning process to produce an optimal plan that meets the dose-volume constraints on the target volumes and normal tissues outlined below. Coverage of the reconstructed breast/chest wall can be with partially wide tangents, multiple intensity modulated beams or a combination of matching electrons and photons. This trial is specifically evaluating toxicity and cosmesis; therefore, we have set tight constraints on maximum doses.

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

Chest wall CTV to PTV expansion is a range of 5-7mm, based on institutional practice and technical capabilities.

The following volumes are to be delineated:

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

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

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

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

Expanders, implants or autologous tissue present for reconstruction will be included in the Chest Wall CTV. The degree of fluid expansion present is per the treating physician's discretion. The expander should remain at the same expansion from the time of CT simulation and through the entire course of radiation treatment. Any changes in the expansion volume will require repeat CT simulation and planning.

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

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

The use of **skin bolus** is often recommended for post-mastectomy irradiation, but ultimately is per the treating physician's discretion to individualize to the patient's treatment and radiotherapy plan. If using bolus, the skin dose should follow the same constraints as the Chest wall PTV Eval and should be utilized in the planning system dose calculations.

Regional Nodal Radiation:

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

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

Axillary CTV: The extent of the axilla to be targeted for regional nodal irradiation will depend on how much of the axilla has been dissected.

The axillary CTV consists of the portion of the axilla that remains "undissected". When an axillary node dissection has been done, the inferior border of the axillary CTV will be the most cephalic extent of the dissection. Review of the operative report, postoperative changes on the planning CT, and discussion with the patient's surgeon can be used for determining the most cephalic extent of the dissection and inferior border of the axillary CTV. In cases in which axillary has been inadequately dissected (less than 6 nodes removed), the full axilla including levels I and II should be included in the axillary CTV.

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

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

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

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

Structure List for Right Breast

Description	**Planning System Name**
Mastectomy Scar GTV	Scar_R
Mastectomy Scar CTV	CTV_Scar_R
Chest Wall CTV	CTV_CW_R
Chest Wall PTV	PTV_CW_R
Chest Wall PTV Eval	PTV_CW_EVA_R
Supraclavicular CTV	CTVn_SCL_R
Supraclavicular PTV	PTVn_SCL_R
Axillary CTV	CTVn_Ax_R
Axillary PTV	PTVn_Ax_R
Internal Mammary Node CTV	CTVn_IMN_R
Internal Mammary Node PTV	PTVn_IMN_R
Ipsilateral Lung	Lung_R
Contralateral Lung	Lung_L
Heart	Heart
Contralateral Breast or Chest Wall	Breast_L
Thyroid	Thyroid

Structure List for Left Breast

Description	**Planning System Name**
Mastectomy Scar GTV	Scar_L
Mastectomy Scar CTV	CTV_Scar_L
Chest Wall CTV	CTV_CW_L
Chest Wall PTV	PTV_CW_L
Chest Wall PTV Eval	PTV_CW_EVA_L

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

In cases in which patients have undergone thyroidectomy, contour of the thyroid will not be required for submission. Contralateral breast (R or L) will be used to generically name the contralateral intact breast, reconstructed breast or unreconstructed chest wall.

7.4.3 Dose-Volume Histogram (DVH) Analysis.

ARM I (Standard Fractionation)

Chest wall:

Preferred: ≥ 95% of the chest wall or breast PTV Eval contour that falls within the tangential treatment fields will receive ≥ 47.5 Gy which is 95% of the chest wall or breast prescribed dose of 50 Gy.

Acceptable: ≥ 90% of the chest wall or breast PTV Eval contour that falls within the tangential treatment fields will receive ≥ 45 Gy which is ≥ 90% of the whole breast prescribed dose of 50 Gy.

Maximum Dose to Chest wall.

Photon only plan to treat the chest wall and internal mammary chain:
Less than 10cc of PTV Eval will receive ≥ 107% dose or 53.5 Gy for a prescribed breast/chest wall dose of 50 Gy. Less than 0.03cc can receive > 115% of dose, 57.5Gy.

Composite photon/electron plans to treat the chest wall and internal mammary chain:
Less than 10cc of PTV Eval will receive ≥ 115% dose or 57.5 Gy for a prescribed dose of 50 Gy. Less than 0.03cc can receive 130% of the dose, 65 Gy.

Supraclavicular (SCL):

Preferred: ≥ 95% of the SCL PTV will receive ≥ 95% (47.5 Gy) of the prescribed dose of 50 Gy.

Acceptable: ≥ 90% of the supraclavicular PTV will receive ≥ 90% (45Gy) of the prescribed dose of 50 Gy.

***Maximum dose*:** Less than 0.03cc can receive greater than 110% (55 Gy).

Axillary volume:

Preferred: ≥ 95% of the Axillary PTV will receive ≥ 95% (47.5 Gy) of the prescribed dose of 50 Gy.

Acceptable: ≥ 90% of the Axillary PTV will receive ≥ 90% (45 Gy) of the prescribed dose of 50 Gy.

***Maximum dose*:** Less than 0.03cc can receive greater than 110% (55 Gy).

Internal mammary nodal (IMN) volumes:

Preferred: ≥ 90% of the IMN PTV will receive ≥ 90% (45 Gy) of the prescribed dose of 50 Gy.

Acceptable: ≥ 90% of the IMN PTV will receive ≥ 80% (40 Gy) of the prescribed dose of 50 Gy.

Contralateral breast:

Preferred: Less than 10% of the contralateral breast receives >3Gy.

Acceptable: Less than 10% of the contralateral breast receives > 10 Gy

Note: In patients with a contralateral mastectomy there is no contralateral breast tissue and there is no specified constraint on the contralateral chest wall.

Ipsilateral Lung:

Preferred: ≤ 35% of the ipsilateral lung should receive ≥ 20 Gy.

Acceptable: ≤ 40 % of the ipsilateral lung should receive ≥ 20 Gy.

Contralateral Lung:

Preferred: ≤ 10% of the contralateral lung should receive 5 Gy or more.

Acceptable is ≤ 15% of the contralateral lung should receive 5 Gy or more.

Heart:

Preferred ≤ 10% of the whole heart should receive ≥ 25 Gy for left-sided breast cancers, and ≤ 2% of the heart should receive ≥ 25 Gy for right-sided breast cancers.

Acceptable: ≤ 10% of the whole heart should receive ≥ 30 Gy for left-sided breast cancers, and ≤ 2% of the heart should receive ≥ 30 Gy for right-sided breast cancers.

Preferred: Mean heart dose should be ≤ 3 Gy.

Acceptable is a mean hart dose ≤ 5 Gy.

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

ARM II (Hypofractionation Fractionation)

Chest wall:

Preferred: ≥ 95% of the chest wall or breast PTV Eval contour that falls within the tangential treatment fields will receive ≥ 40.4 Gy which is 95% of the chest wall or breast prescribed dose of 42.56 Gy.

Acceptable: ≥ 90% of the chest wall or breast PTV Eval contour that falls within the tangential treatment fields will receive > 38.3 Gy which is ≥ 90% of the whole breast prescribed dose of 42.56 Gy.

Maximum Dose to Chest wall.

Photon only plan to treat the chest wall and internal mammary chain:

Less than 10cc of PTV Eval will receive ≥ 107% dose or 45.55 Gy for a prescribed breast/chest wall dose of 42.56 Gy. Less than 0.03cc can receive > 115% of dose, 48.94 Gy.

Composite photon/electron plans to treat the chest wall and internal mammary chain:

Less than 10cc of PTV Eval will receive ≥ 115% dose or 48.94 Gy for a prescribed dose of 42.56 Gy. Less than 0.03cc can receive 130% of the dose, 55.33 Gy.

Supraclavicular (SCL):

Preferred ≥ 95% of the SCL PTV will receive ≥ 95% (40.4 Gy) of the prescribed dose 42.56 Gy.

Acceptable: ≥ 90% of the supraclavicular PTV will receive ≥ 90% (38.3 Gy) of the prescribed dose 42.56 Gy.

***Maximum dose*:** Less than 0.03cc can receive greater than 110% (46.8 Gy).

Axillary volume:

Preferred: ≥ 95% of the Axillary PTV will receive ≥ 95% (40.4 Gy) of the prescribed dose.

Acceptable: ≥ 90% of the Axillary PTV will receive ≥ 90% (38.3 Gy) of the prescribed dose 42.56 Gy.

***Maximum dose*:** Less than 0.03cc can receive greater than 110% (46.8 Gy).

Internal mammary nodal (IMN) volumes:

Preferred: ≥ 90% of the IMN PTV will receive ≥ 90% (38.3 Gy) of the prescribed dose 42.56 Gy.

Acceptable: ≥ 90% of the IMN PTV will receive ≥ 80% (34 Gy) of the prescribed dose of 42.56 Gy.

Contralateral breast:

Preferred: Less than 10% of the contralateral breast receives > 3Gy.

Acceptable: Less than 10% of the contralateral breast receives > 10 Gy

Note: In patients with a contralateral mastectomy there is no contralateral breast tissue and there is no specified constraint on the contralateral chest wall.

Ipsilateral Lung:

Preferred: ≤ 35% of the ipsilateral lung should receive ≥ 18 Gy.

Acceptable: ≤ 40 % of the ipsilateral lung should receive ≥ 18 Gy.

Contralateral Lung:

Preferred: ≤ 10% of the contralateral lung should receive 4.8 Gy or more.

Acceptable is ≤ 15% of the contralateral lung should receive 4.8 Gy or more.

Heart:

Preferred: ≤ 10% of the whole heart should receive ≥ 22.5 Gy for left-sided breast cancers,

and 2% of the heart should receive ≥ 22.5 Gy for right-sided breast cancers.

Acceptable: ≤ 10% of the whole heart should receive ≥ 27 Gy for left-sided breast.

cancers, and 2% of the heart should receive ≥ 27 Gy for right-sided breast cancers.

Preferred: mean heart dose should be ≤ 300 cGy.

Acceptable is ≤ 500 cGy.

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

7.5 Radiation Therapy Quality Assurance

Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan and dose files. This study uses TRIAD for RT data submission. Use of TRIAD requires several preliminary steps. See Section 4.2. for details. Additional information is available at: [redacted]

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

Any items listed below that are not part of the digital submission may be included with the transmission of the digital RT data.

All required data should be submitted within 3 days of the start of radiotherapy for on-treatment review. In the event that a site submits plans for two or more cases requiring major revisions or having unacceptable deviations, the site may be asked to submit plans prior to treatment for subsequent patients.

Within 3 days of the start of radiotherapy, the following data should be submitted for on-treatment review:

7.5.1 Treatment Planning System Output

- RT treatment plan including CT, structures, dose, and plan files. These items are included in the digital plan.
- Dose volume histograms (DVH) of the GTV, chest wall, heart. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVH's are included in the digital plan.
- Digitally reconstructed radiographs (DRR) for each treatment field. Please include two sets, one with and one without overlays of the target volumes and organs at risk. Submission of DRR's is not required for IMRT.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

7.5.2 Supportive Data

The following data is to be submitted to IROC Rhode Island:

- Copies of operative & pathology reports for mastectomy/SLN/ALND/Plastic Surgery procedures.
- Prescription sheet for entire treatment.
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by IROC Rhode Island and the radiation oncology reviewers.

7.5.3 Forms

The following forms are to be submitted to IROC Rhode Island:

- RT-1 Dosimetry Summary Form

Within 21 days of the completion of radiotherapy, the following data shall be submitted for all patients:

- The RT-2 Radiotherapy Total Dose Record Form
- A copy of the patient's radiotherapy record including the prescription, and the daily and cumulative doses to all required areas.
- Documentation listed above showing any modifications from the original submission.

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

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

[redacted]

7.5.4 Definitions of Deviations in Protocol Performance

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

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

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

7.5.5 Definitions of Deviations in Volumes Drawn

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

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

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

8.0 DOSE AND TREATMENT MODIFICATIONS

Radiation doses should not be modified and compliance with the protocol will be determined as defined above, by the ideal and acceptable dose constraint criteria. Patients may occasionally require treatment breaks, which should be kept to a minimum. Treatment breaks of up to 5 treatment days will be considered acceptable. Treatment breaks of greater than 5 treatment days are strongly discouraged.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. However, CTCAE v5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018. The CTCAE is available at [redacted]
Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures. Radiation-related CTCAE toxicity assessment will be assessed as a secondary endpoint in both acute and late affects.

9.1 Routine Adverse Event Reporting

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

Acute Adverse Events: Acute adverse events, will be scored per CTCAE 4.0 regardless of attribution. Attribution will however be collected for separate analysis.

Late Radiation Adverse Events: Late radiation complications will be defined as those that are present ≥6 months after the final dose of radiation and include CTCAE 4.0 grade 3+:

9.2 Solicited Adverse Events:

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

9.2.1 Radiation Therapy Complications:

CTCAE v4.0 Term	CTCAE v4.0 System Organ Class (SOC)
Fibrosis, deep connective tissue	Musculoskeletal and connective tissue disorders
Superficial soft tissue fibrosis	Musculoskeletal and connective tissue disorders
Chest wall pain	Musculoskeletal and connective tissue disorders
Joint range of motion decreased	Musculoskeletal and connective tissue disorders
Wound Infection	Infections and infestations
Fatigue	General disorders and administration site conditions
Dermatitis radiation	Injury, poisoning and procedural complications
Wound complication	Injury, poisoning and procedural complications
Wound dehiscence	Injury, poisoning and procedural complications
Lymphedema	Vascular disorders
Telangiectasia	Skin and subcutaneous tissue disorders
Hypothyroidism	Endocrine Disorders
Myocardial Infarction	Cardiac disorders
Cardiac disorders – Other specify*	Cardiac disorders
Pulmonary fibrosis	Respiratory, thoracic and mediastinal disorders
Brachial Plexopathy	Nervous system disorders
Peripheral motor neuropathy	Nervous system disorders
Peripheral sensory neuropathy	Nervous system disorders
Treatment related secondary malignancy	Neoplasms benign, malignant and unspecified (including cysts and polyps)

* Specific cardiac events, if and when they occur will be recorded on the Adverse Events: Other form.

9.2.2 Non CTCAE RT Associated Complications:

a) Shoulder stiffness (occasional) (Grade 1-3)

b) Rib fracture (rare) (Grade 1-3)

9.2.3 Non CTCAE Reconstruction Associated Complications:

The primary endpoint of this trial is the reconstruction complication rate at 24 months after radiation that requires hospitalization or re-operation. (Complications related to the contralateral breast will be collected but will not count towards the assessment of the primary endpoint, ipsilateral breast complications will be counted towards the primary endpoint). This is an adverse event rate not well characterized by the CTCAE terminology, and therefore will be recorded separately from CTCAE toxicity as follows:

a. Capsular contracture (Baker grades III-IV would only count towards the primary endpoint)

   Definition of Capsular contracture grades (to be captured in Rave)

   - Grade I — the breast is normally soft and appears natural in size and shape
   - Grade II — the breast is a little firm, but appears normal
   - Grade III — the breast is firm and appears abnormal
   - Grade IV — the breast is hard, painful to the touch, and appears abnormal

b. Complete failure of the implant/skin flap

c. Unplanned admission for reconstruction related issue(s) including but not limited to infection, wound healing complication or pain

d. Unplanned return to the operating room for reconstruction related issue including but not limited to infection, prosthesis exposure, failed reconstruction, implant removal, wound healing complications or contracture management

Routine revisions, such as dog-ear corrections, fat grafting and revising the contralateral breast will not be scored as an adverse reconstruction event. Additionally, a contracture that is corrected when the tissue expander is exchanged for an implant or autologous tissue flap will not be scored as an event.

9.3 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Attribution refers to radiation and reconstruction. Adverse events attributed to chemotherapy need not be reported. Questions about routine reporting should be directed to the Data Manager.

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

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

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

9.4 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Investigational Drug Branch (IDB), the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site: [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).

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

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

9.4.1 Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial ≤ 30 Days of the Last Administration

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

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

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

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

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

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

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting detailed below.

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Adverse events attributed to chemotherapy need not be reported.
- Grade 1-3 nausea or vomiting and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 or 4 nausea or vomiting does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 fatigue and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 or 4 fatigue does not require AERS reporting, but should be reported via routine AE reporting

- Grade 1-3 radiation dermatitis and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 or 4 radiation dermatitis does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 lymphedema and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 lymphedema does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 pneumonitis and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 or 4 pneumonitis does not require AERS reporting, but should be reported via routine AE reporting
- Grade 2-3 acute coronary syndrome or myocardial infarction and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 or 4 acute coronary syndrome or myocardial infarction does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 chest pain and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 chest pain does not require AERS reporting, but should be reported via routine AE reporting
- Grade 2-3 wound infection and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 or 4 wound infection does not require AERS reporting, but should be reported via routine AE reporting
- Reporting of cases of secondary AML/MDS is to be done using the NCI/CTEP Secondary AML/MDS Report Form. New primary malignancies should be reported using Form Notice of New Primary.
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- 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.

  Secondary Malignancy:

  A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

  CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

  - Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy

  Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

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 unless otherwise specified.

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.

- CTCAE 4.0 grading listed where applicable.

  Grade 4 toxicities that reflect life threatening events require CTEP-AERS reporting. Grade 4 wound healing per CTCAE can including wound healing that requires a major flap reconstruction. As this is part of breast reconstruction, this will not be recorded as a CTCAE complication. Grade 1-3 toxicity does not need CTEP-AERS reporting, but should be reported via routine AE reporting.
- CTEP-AERS reports should be submitted electronically.
- Pregnancy loss
  - Pregnancy loss is defined in CTCAE as "Death in utero."
  - Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.
  - A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEPAERS recognizes this event as a patient death.
  - A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.
- When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and submitted, along with any additional medical information (form is available on the CTEP website at [redacted] The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

10.0 MEASUREMENT OF EFFECT

10.1 Ipsilateral Reconstruction Complications

Reconstruction complications will be defined as:

a. Capsular contracture (Baker Grade III or IV only)

b. Complete failure of the implant/skin flap

c. Unplanned admission for reconstruction related issue(s) including but not limited to infection, wound healing complication or pain

d. Unplanned return to the operating room for recon related issue including but not limited to infection, prosthesis exposure, failed reconstruction, implant removal, wound healing complications or contracture management

Note: Complications related to the contralateral breast will be collected but will not count towards the assessment of the primary endpoint, ipsilateral breast complications will be counted towards the primary endpoint.

10.2 Acute and Late Radiation Complications

Acute Adverse Events: Acute adverse events, will be scored per CTCAE 4.0 regardless of attribution. Attribution will however be collected for separate analysis.

Late Radiation Adverse Events: Late radiation complications will be defined as those that are present ≥6 months after the final dose of radiation and include CTCAE 4.0 grade 3+:

10.3 Criteria for Disease Response

Local and regional recurrences: A recurrence will be classified as local if it recurs on the chest wall (local) or reconstructed breast. Local regional recurrence will be classified for the axillary, supraclavicular, infraclavicular or ipsilateral internal mammary lymph nodes, and distant recurrence for elsewhere.

10.3.1 Local Recurrence

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

10.3.2 Regional Recurrence

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

10.3.3 Distant Recurrence

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

10.3.4 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 chest wall.

10.3.5 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.

10.3.6 Death

Underlying cause of death is to be reported.

10.4 Patient Reported Outcomes

Patient-reported assessments of cosmesis, lymphedema, well-being, and satisfaction with treatment will be collected at the time points listed below. Each questionnaire that will be administered in this study is described in the following sections.

These self-reported questionnaires will require approximately 30 to 45 minutes for completion at all time points. We estimate The BREAST-Q questionnaire requires 10-15 minutes for completion, the Was It Worth It questionnaire requires 1-3 minutes, the lymphedema questionnaires require 5-10 minutes, the photography requires 5-10 minutes, and the health care utilization 5-10 minutes.

10.4.1 Breast Q survey (Appendix II)

We will be using the Breast Q survey tool (section V 2.0) to assess patient-reported cosmesis, well-being, and satisfaction. [81-83] This tool has been validated for use in patients before and after mastectomy with reconstruction, and is provided free of charge for academic research. We will be using the Breast Q Post Mastectomy or Post Reconstruction (if already reconstructed) Module at

prior to radiation therapy and the Breast Q Post Reconstruction Module at 2 and 5 years (+/- 2 months) after radiation finishes. There are 62 items in the post-mastectomy module and 116 items in the post-reconstruction module (but an individual patient will only complete those that apply to her specific type of reconstruction). These modules are currently available in 16 languages, but for this study we will be limiting enrollment to patients who can consent to participation in English language only (for US), in addition to patients who can read and comprehend French, from CCTG institutions. The conceptual framework of the BREAST-Q modules is comprised of two overarching themes, which are health-related quality of life (QOL) and patient satisfaction.

Within QOL, there are three scales: Physical, Psychosocial and Sexual Well-being. Within the Psychosocial Well-being scale for patients with breast reconstruction planned or already performed, there are items that ask about body and a woman's confidence in social settings. Other items cover emotional health and self-esteem. Within the Sexual Well-being scale, there are items that ask about feelings of sexual attractiveness when clothed and unclothed and sexual confidence as it relates to one's breasts, as well as how comfortable or at ease a woman feels during sexual activity. Within the Physical Well-being scales (one for Upper Body and one for Abdomen and Trunk), there are questions asking about pain, activity limitations, and sleep problems due to discomfort, as well as abdominal discomfort, bloating, bulging, and difficulty doing certain activities due to abdominal weakness.

Within patient satisfaction, there are three other scales: Satisfaction with breasts/nipples/abdomen, Satisfaction with overall outcome and Satisfaction with Care. There are three breast/nipple/abdomen satisfaction scales that are administered depending on the type of reconstruction: in the Satisfaction with breasts scale, there are questions regarding how comfortably bras fit, and how satisfied a woman is with her breast area both clothed and unclothed. There are also implant-specific items (e.g., amount of rippling that can be seen or felt). In the Satisfaction with nipples scale (to be completed only by those who underwent nipple reconstruction), there are items covering shape, color, projection and how natural the reconstructed nipple looks. In the Satisfaction with abdomen scale (to be completed only following autologous tissue breast reconstruction with TRAM or DIEP flap), there are items asking about overall appearance as well as position of navel (belly button) and scars. In the Satisfaction with outcome scale, there are items asking about whether or not expectations were met with respect to the aesthetic outcome and the impact reconstruction has had upon her life as well as satisfaction with the decision to have reconstruction (e.g. "I would do it again"). The Satisfaction with Care scale will not be included in this study.

Each scale can be used independently and scored separately. The BREAST-Q scoring software, QScore, transforms patient-reported data into summary scores ranging from 0-100 with a higher number meaning better quality of life or higher satisfaction on the various scales.

BREAST Q questionnaires are currently completed with pencil and paper. Patients will be asked to complete these at a clinic visit, but patients who are unable to receive and/or complete this survey in clinic will be allowed to receive and/or return this survey by mail.

10.4.2 Was It Worth It Questionnaire (Appendix V)

The Was It Worth It questionnaire will assess satisfaction with participation in a research trial. It will be administered at 24 months (+/- 2 months) after the final dose of radiation.

10.4.3 EuroQol EQ-5D-3L Questionnaire (Appendix VI) [111, 112]

The EQ-5D-3L, a 5-item functional health status survey and single utility item is included to compare the quality-adjusted life years between the treatment arms. It will be collected prior to radiation and at 6, 12, 18, and 24 months after radiation therapy.

The EQ-5D is a measure of health status for use in evaluating health and healthcare. The EQ-5D-3L is comprised of 2 pages: the EQ-5D descriptive system (page 1) and the EQ visual analogue

scale (EQ VAS) (page 2). It provides a simple descriptive profile of five functional dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It generates a single index value for health status on which full health is assigned a value of 1 and death a value of 0. Thus, the index can be used to obtain a utility for these dimensions for use in economic analyses. The EQ-5D has been specially designed to complement other quality of life measures such as the SF-36, or cancer-specific measures. Each dimension has three levels designated simply as 'no problem', 'some problem', or 'extreme problem', with patients checking the level most descriptive of their current level of function on each dimension. Five dimensions, each with three levels, yield 243 possible distinct health states comprising the classification system. The classification system has been assigned different standardized scores derived through population-based samples of respondents who assign values to subsets of the 243 states using the anchoring labels noted above. For example, health state 11212 represents a patient who indicates some problems on the usual activities and anxiety/depression dimensions. A set of valuation weights has thus been derived from a U.S. sample. [113] The Agency for Healthcare Research and Quality has funded a study to develop definitive weights. EQ-5D is designed for self-completion by patients and has been used extensively in mailed surveys. It is cognitively simple, taking no more than a few minutes to complete.

10.5 Lymphedema

Lymphedema assessments (i.e., bilateral arm circumference measurements) will be administered before radiation, 6 months after radiation and then again at 2 years after completion of radiation therapy. Body mass index (BMI) will also be ascertained. Lymphedema questionnaires will be completed as described in Section 10.5.2. Patients who develop a new or recurrent breast cancer will discontinue the arm lymphedema assessments.

10.5.1 Clinical Assessment

All planned lymphedema evaluations will include clinical assessment for signs and symptoms of lymphedema. Any patient complaining of “arm swelling” or “heaviness” or showing signs of extremity swelling (≥ 2 cm difference between upper extremities at any measurement point) will be treated according to current practice guidelines and referred to a lymphedema health care provider. In addition, patients will be instructed to call their oncologist if they develop any new arm symptoms during the periods between planned assessments. Such patients will be scheduled for immediate evaluation and arm measurements.

Arm Measurement: Circumferential measurement of limb volume will be performed on both affected and non-affected arms. Patients will sit with the arms resting horizontally palms-down on a bedside table placed at a level slightly below the axilla. The patients will be instructed to wear loose sleeves or short sleeves/sleeveless tops and to remove any arm jewelry prior to the measurement. Measurements will be taken at the wrist, half way between the wrist and antecubital fossa (below the elbow), at the antecubital fossa, half way between the antecubital fossa and the axilla, and at the axilla. In all cases, the plane of the tape around the arm will be held perpendicular to the long axis of the arm and perpendicular to the floor. The tape will be held snugly around the body part without indenting the skin or compressing subcutaneous adipose tissue. If gaps between the skin and tape are seen in some individuals, tension should not be increased to reduce the gap. Arm measurements and other required data will be recorded on the Arm circumference measurement case report form (Appendix IV) which is to be completed by the local study coordinator. The standard formula (based on cylindrical slices) will be utilized in this study to calculate volume (V) from circumference (U) measures.

PowerPoint slides located on the A221505 study page will provide instructions on how to perform these measurements. The procedures used in CALGB 70305 will be followed in this study.

Arm Lymphedema: A patient will be considered to have mild lymphedema if she has symptomatic arm swelling or heaviness with less than a 10% increase in volume of the ipsilateral arm from pre-radiation volume.

We will consider two different measures of arm lymphedema as secondary endpoints in this study. As a second measure of arm lymphedema, we will consider the percent change in ipsilateral arm volume post-radiation from its pre-radiation volume. The impact of lymphedema based on extent of surgery (sentinel vs. axillary dissection) has been reported elsewhere and therefore will not be focus of this study.

Breast Lymphedema: While upper extremity lymphedema is a recognized complication following axillary surgery for breast cancer, breast lymphedema can also occur and be associated with significant morbidity. To date, this condition has not been highlighted primarily because the objective measurement and diagnostic criteria have largely been unavailable. The most common criteria used are based on clinical signs of diffuse skin edema and erythema. Reconstructed breast edema will be captured in the CTCAE late morbidity reporting as well as in the cosmesis evaluation and the LBCQ questionnaire (Section 10.5.2).

10.5.2 Patient Completed Lymphedema Questionnaires (Appendix III)

The Lymphedema and Breast Cancer Questionnaire (LBCQ) short form and Breast Lymphedema (BLE) Symptom Survey will be offered to all patients, and administered before radiation, 6 months after radiation and then again at 2 and 5 years after completion of radiation therapy.

The Lymphedema and Breast Cancer Questionnaire (LBCQ) short form consists of 19 symptom-related questions. Armer et al. initially developed, piloted, and revised the LBCQ-Part I as a semi-structured interview tool to assess signs and symptoms of lymphedema [52]. Subsequently, expert patient educators, clinicians, and researchers reviewed and revised the LBCQ for clarity, simplicity of format, and complete coverage of the symptom domain. The final LBCQ Part I ended up consisting of 19 symptom-related questions to which patients respond to the interviewer with "yes/no" answers regarding whether the symptom is currently present (today or within the past month) or has been present at any point in the past year. Scores are calculated for the frequency of the total number of current symptoms and the total number of symptoms in the past year. Validity of this instrument was confirmed through studies that found it was able to differentiate healthy women and women with known breast cancer lymphedema. The instrument was also found to be predictive of the development of limb swelling in a sample of breast cancer survivors with yet-undetermined lymphedema status. [67] The LBCQ questionnaire should be administered by trained institutional research staff. However, if the patient self-completes the questionnaire, a member of the study research team who is knowledgeable about the study, should be available to instruct, answer questions, and review the questionnaire for completeness.

The **Breast Lymphedema (BLE) Symptom Survey** has also been included to rate severity of symptoms of the chest wall or reconstructed breast for heaviness, discomfort, redness, swelling and associated degree of distress using a 10-point scale ('Not at all'=0 to 'A lot'=10). This has been extrapolated in the reconstructed breast setting from women undergoing breast conservation. In a prospective study of 124 women who underwent breast-conserving operations, women who were clinically diagnosed with BLE reported more symptoms than women without BLE (mean 2.6 versus 1.3, $p < 0.0001$). Two or more symptoms included on the questionnaire were reported by 81% of women with BLE compared to 35% of women without BLE. Women with BLE also had significantly higher severity scores for breast heaviness, redness, and swelling. By physical exam, 100% of women with BLE had skin edema compared to 11.6% of those without BLE, ($p<0.0001$). Similarly, breast erythema was seen in 79% of those with BLE compared to 13% without BLE, $p<0.0001$[68].

10.6 Photographic Cosmetic Assessment

An important outcome of this study is the cosmetic outcome of hypofractionated radiation versus conventional radiation and the risks of late radiation morbidity. These side effects include telangiectasia, breast fibrosis, scar retraction and skin pigmentation changes, which may all affect the cosmetic result. As this is not a blinded study, cosmetic assessment will be by digital photography reviewed by a Central Adjudication Committee unaware of treatment allocation evaluating late radiation morbidity.

Confidential bilateral digital photographs (excluding the face) will be taken with a digital camera:

1) Standing, anterior photo to show both breasts with the arms at 45° from the body and
2) Close up of treated area to show the surgical scar and surrounding reconstructed tissue at 24 months post radiation.

Photographs will be captured of both breast/reconstructed chest walls at the following time points:

- Before radiation, only for patients with immediate reconstruction
- 24 months after the completion of radiation for all patients.

Photographs of both breasts will be collected as above and reviewed by a blinded Central Adjudication Committee according to the modified EORTC Cosmetic Rating System. Study participants will be identified only by study ID number of their photographs to ensure confidentiality. De-identified photographs will be submitted to IROC Rhode Island where they will be prepared for review and archived with the patient record. See section 6.3 for instructions for submission of photographs. The review process has been used extensively in the past, including in the recent Canadian RAPID study of partial breast radiation. The treated breast will be compared to the intact opposite breast or contralateral reconstructed chest wall. For patients who have their final reconstruction performed prior to starting radiation, there will also be pre-radiation photographs taken. Patients who develop an ipsilateral breast cancer or lymph node recurrence before the 24 month photography assessment will not be assessed. We will use the modified EORTC digital photographic method used in the Canadian RAPID trial. This approach has been shown to be reliable in intact breast patients and is validated in detecting the effects of radiation morbidity. [45-47]. Unfortunately, there are no validated photographic assessment tools in reconstructed breast patients.

The confidential photographs will be assembled into presentation format to allow for efficient review by the Central Adjudication panel. The online training module will be reviewed and utilized by the panel. Two panels of 3 multidisciplinary experts will form the Central Adjudication panel, including representatives from the disciplines of radiation oncology, breast surgery and plastic surgery. Once all photographs are collected there will be a minimum of 1-2 in-person meetings by panels to review and score the photographs. This method has been used extensively in the past, including the recent NSABP B-39 trial and the Canadian RAPID partial breast trial, and found to be valid and reliable. The Central Adjudication panel includes members with significant experience in conducting photographic cosmetic assessment in prior studies.

10.7 Health Economic Analysis

A reduction in number of radiation treatments and thereby number of visits to the radiation therapy department will benefit patients directly, both in terms of reduced direct and indirect healthcare costs. Direct healthcare costs are expected to go down because of an expected reduction in health care utilizations services (e.g., office visits, emergency room visits, inpatient admissions). With short-course treatment patients may be able to take less time off from work and/or return to work faster. Potential improvements in cosmetic-outcomes and side effects of radiation therapy with short-course therapy could also translate into a reduction in utilization of health care services, further enhancing the economic impact of hypofractionation. Indirect costs are also expected to be lower for the intervention arm because patients in this arm are expected to resume normal activities sooner. This in turn would help save family caregiver time as well as the cost of dependent care, which will further add to the saving in indirect costs. Therefore, robust measurement of the patient resources used to receive radiation therapy and utilization of health services is a critical component of this randomized multicenter international trial.

To assess patient resources used for receipt of radiation therapy and recovery, patients will be asked to complete the Health Care Expense Questionnaire which will take about 20 minutes. They will be given a **Health Care Expense Diary and Questionnaire booklet** (Appendix VII) with question domains to be filled out during radiation therapy and up to 8 weeks after radiation in order to help improve recall for completion of this questionnaire. They will use information recorded in the Health Care Expense Diary to complete and submit the Health Care Expense Questionnaire at the 2-8 week clinic visit.

Upon completion of radiation therapy patients will be given the **Health Care Utilization Diary** (Appendix VIII) to record any clinic visits, visits to emergency rooms, to physical therapists, and/or any other health care services used, as well as any hospital admissions that occur in the year that following radiation therapy. At the 12-month post-radiation visit, patients will be asked to report the utilization of health care resources in the interval between radiation completion and the end of 12-month follow-up using the completed Health Care Utilization Diary.

Treating institutions in the U.S. are also instructed to submit CPT code charges generated from the time of registration to 12 months after the completion of radiation therapy. These will be used to estimate a standardized direct cost of care.

Questions are adapted from the Medical Expenditure Panel Survey-Household Component (MEPS-HC) created by AHRQ [redacted] The questionnaire can be found in Appendix VII.

11.0 END OF TREATMENT/INTERVENTION

11.1 Duration of Treatment

Radiation therapy is to be given 5 days a week for 5-6 weeks in Arm 1 and 5 days a week for 3-4 weeks in Arm 2, per Section 7.4.

11.2 Criteria for discontinuation of protocol treatment

Radiation treatment will continue unless one of the following criteria applies:

- Disease progression or relapse
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the treating physician
- Patient withdrawal or non-compliance
- Patient receives alternative treatment (non protocol treatment that replaces standard RT or RT not per protocol) before or during protocol treatment period
- Patient experiences reconstruction related complications to the ipsilateral breast prior to start of radiation. No further follow up will be required for these patients (see Section 11.4.2).

11.3 Follow-up

11.3.1 Duration of follow up

Patients who complete radiation therapy and breast reconstruction-will be followed as outlined in Section 5.0 until disease recurrence, contralateral breast cancer, or a non-breast second primary cancer; or until an alternative treatment is given for up to 15 years after the end of radiation therapy. All follow up (including survival) done after 5 years will be gathered by record review only.

11.3.2 Follow up for patients who do not complete radiation and breast reconstruction

Patients who complete radiation per protocol, but who do not complete reconstruction will also be followed as outlined in Section 5.0 until disease recurrence, contralateral breast cancer, or a non-breast second primary cancer; or until an alternative treatment is given for up to 15 years

after the end of radiation therapy. All follow up (including survival) done after 5 years will be gathered by record review only.

Patients who experience disease recurrence, contralateral breast cancer, or a non-breast second primary cancer, or alternative treatment will discontinue protocol therapy and no further follow up will be required.

11.4 Managing Ineligible Patients and Registered Patients Who Never Receive Protocol Intervention

11.4.1 Ineligible patients

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

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

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

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

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

- Baseline, off treatment, and end of study form required. See the Data Submission Schedule accompanying the All Forms Packet.
- * Patients who experience reconstruction related complications before the start of radiation will not receive protocol treatment, and the end of study form will be completed for these patients.

11.4.3 Follow-up for patients who are registered, but withdraw after starting study treatment

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar until disease recurrence, contralateral breast cancer, or a non-breast second primary cancer or alternative treatment.

11.5 Extraordinary Medical Circumstances

If at any time the constraints of this protocol are detrimental to the patient's health, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar until disease recurrence, contralateral breast cancer, or a non-breast second primary cancer or alternative treatment.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design

This is a randomized, two-arm, un-blinded, non-inferiority trial comparing the impact of hypofractionated dosing (vs. standard dosing) of radiation on the 24-month breast reconstruction complication rate.

12.2 Sample Size, Accrual Time and Study Duration

Our target sample size will be 792 evaluable patients (396 in each arm). To account for 10% drop-out due to cancelations or protocol deviations, our target accrual is 880 patients (440 per arm) (90% of 880 is 792).

The study design is a randomized, un-blinded, non-inferiority trial. It is assumed that the two-year breast reconstruction complication rate for the control arm (Arm 1: standard fractions) is 25%. Other assumptions for the sample size determination include:

- alpha (one-sided) = 0.025
- power = 90%
- non-inferiority margin: the absolute increase in the proportion of patients who experience
- a breast reconstruction complication within two-years is 10% above that of the control arm.
- one interim analysis (when 30% of the information is obtained) for futility

Under an alternative hypothesis that the true rates in the two arms are equal, a sample size of 792 (396 per arm) evaluable patients would give us 90% power to reject the null hypothesis of inferiority. The final analysis will take place after all patients have reached two years post-radiation. The anticipated accrual period is approximately 30 months, and the total study duration is approximately 60 months. We anticipate being able to accrue approximately 30 patients per month based on our best estimate extrapolated from recently closed intact breast trials looking at similar fractionations. It should be noted that if we instead assumed a complication rate of 50% in the control arm (the most statistically conservative, in terms of sample size), the above sample size would still give us approximately 80% power to reject the null hypothesis of inferiority (again with one-sided alpha of 0.025).

12.3 Statement of Primary Endpoint

12.3.1 Primary Endpoint

Our primary endpoint is the rate of breast reconstruction complications, defined in Section 10.1.

Routine revisions, such as dog-ear corrections, fat grafting, and contralateral breast revision will be recorded, but not counted towards primary endpoint events.

12.3.2 Analysis Plan for Primary Endpoint

The null hypothesis for our primary analysis is that the proportion of patients who experience a breast reconstruction complication within two years after the end of radiation treatment on Arm 2 (hypofractionated dosing) (denoted π_2) will be at least 0.1 higher than the proportion of patients in Arm 1 (denoted π_1) (standard dosing) (i.e. that hypofractionated dosing is inferior to standard dosing). This will be tested using a two-sample test of proportions. In particular, we will calculate the test statistic: $Z = (\pi_1 - \pi_2 + 0.1)/[\pi_1(1- \pi_1)/n_1 + \pi_2(1- \pi_2)/n_2]^{1/2}$, where n_1 and n_2 are the numbers of patients in Arms 1 and 2, respectively.

Interim analysis decision rule

Interim analysis of inferiority of hypofractionated PMRT (futility) as compared to conventional PMRT will be conducted when 30% of patients are enrolled and have reached two years post-radiation. The Lan-DeMets family of alpha and beta spending functions corresponding to the O'Brien-Fleming boundary are used for controlling overall type II error rates. Inferiority of the hypofractionated PMRT will be concluded if p-value > 0.843 (corresponding to $Z < -1.007$). The second stage of this clinical trial shall continue if p-value is ≤ 0.843.

Final analysis decision rule

Final analysis will be conducted when all target patients are enrolled and have reached 2 years post radiation. Non-inferiority of hypofractionated PMRT will be concluded if p-value < .025 (corresponding to Z > 1.96) and inferiority of hypofractionated PMRT will be concluded if p-value ≥.025 (corresponding to Z ≤1.96).

Study Operating characteristics
Simulation studies of 10,000 clinical trials are conducted for the proposed group sequential design. The probabilities of early stopping (at the interim analysis) and empirical powers for various scenarios are summarized in the following table. Of particular interest, assuming that the two-year breast reconstruction complication rate is 25% for the control arm (Arm 1: conventional PMRT) and 35% for the hypofractionated PMRT (Arm 2), where the Arm 2 treatment is inferior to Arm 1, there is a 14.45% chance of stopping the trial early to conclude that hypofractionated PMRT is inferior. In another scenario where the complication rate of the conventional PMRT is 25% and that of hypofractionated is 25%, where the Arm 2 treatment is truly non-inferior to Arm 1, the likelihood of stopping early to conclude inferiority is 0.24% and the likelihood of the trial concluding that hypofractionated PMRT is non-inferior to conventional one is 90.84% (power).

Reconstruction complication rate		Interim analysis conclusion		Early stopping	Final analysis conclusion		Rejection (of H_0) rate
Conventional	Hypofractionated	Noninferior	Inferior		Noninferior	Inferior	
25%	35%	0.00%	14.45%	14.45%	2.37%	83.18%	2.37%
	30%	0.00%	2.86%	2.86%	34.51%	62.63%	34.51%
	25%	0.00%	0.24%	0.24%	90.84%	8.92%	90.84%

It should be noted that the primary analyses will be an intent-to-treat analysis where all patients randomized will be included in the analysis and will be analyzed based on the arm they were randomized to regardless of actual radiation schedule received. This analysis will not be stratified. Due to the random treatment assignment with stratification for the timing of reconstruction and type of reconstruction, it is expected that the baseline patient characteristics, including the planned reconstruction procedures, are roughly balanced across the two treatment arms. A sensitivity analysis stratified by timing and type of reconstruction surgery will be conducted.

The frequency and the proportion of patients who enrolled in the trial prior to reconstruction surgery who did not receive the surgery within 18 months of radiation as specified in the eligibility criteria will be summarized separately by arm. A secondary analysis excluding these patients will be conducted.

12.4 Supplementary/Secondary Analysis Plans

12.4.1 Secondary Objectives

Incidence of acute and late radiation complications based on CTCAE 4.0 toxicity. The proportion of patients with acute or late radiation complications, will be estimated separately by treatment arm and will be compared across the two arms using two-sample test of proportions (Z test) with a two-sided alternative.

Local and local regional recurrence rate: The cumulative incidence of local and local regional recurrence will be estimated separately by treatment arm using the cumulative incidence function treating death as the competing risk and will be compared using Gray's test. In addition, local and local regional recurrence free survival will be summarized for each arm using the Kaplan-Meier estimators, and will be compared using a log rank test.

Reconstruction complication rates based on reconstruction method (autologous +/- implant vs. implant only) and timing of reconstruction received (immediate vs. intent for delayed): Between-arm differences in reconstruction complication rates will be assessed separately within each of the six subgroups based on type and timing of reconstruction. Between-arm differences in complication rates will also be assessed within the two broader subgroups of patients who receive implant only and those who receive autologous based reconstruction. Within each subgroup, the comparison will be done using a two-sample Z test of proportions with a two-sided alternative as described for the primary analysis in Section 12.3.2.

12.4.2 Photographic Cosmetic Assessment

Reconstructed breast photographic cosmetic scores 24 months after radiation with hypofractionated radiation compared to standard fractionation: Two year photographic cosmetic scores will be summarized by treatment arm and will be compared across the treatment arms using a Wilcoxon rank-sum test with a two-sided alternative. The proportions of patients with poor global cosmetic score (defined as a cosmetic score of 3: poor or large difference) at 24 months after radiation will be summarized separately by treatment arm and will be compared using a two-sample test of proportions with a two-sided alternative.

Reconstructed breast photographic cosmetic scores 24 months after radiation based on the method and timing of reconstruction received: Two year photographic cosmetic scores and the proportions of patients with poor global cosmetic score will be assessed separately by timing and method of reconstruction subgroups using similar method described above.

12.4.3 Lymphedema Assessment

Incidence of arm lymphedema by treatment arm: The proportions of patients with arm lymphedema (defined as a change of 10% or greater in ipsilateral arm volume from the pre-RT volume, see also Section 10.3.1 for definition of arm lymphedema) at 2 year post radiation will be summarized and will be compared across the two treatment arms using a two-sample test of proportions (Z test) with a two-sided alternative. Change in ipsilateral arm volume at each of the following time-points: 6, 12, 24 and 60 months post-radiation (relative to pre-RT) will be compared using a two sample t-test with a two-sided alternative. The changes in arm volume at these time points will also be analyzed as a repeated measure using a linear mixed model with patient as the random effect.

12.4.4 Patient Reported Outcomes (PRO) Objectives

Physical well-being, psychosocial well-being, sexual well-being, satisfaction with breast/nipples/abdomen, and satisfaction with overall outcome between the treatment arms at 24 months after radiation: Change in LBCQ and BLE scores at 24 months post-radiation (relative to pre-RT) and patient satisfaction scores as measured by the Breast Q overall outcome scale will be summarized and will be compared across the treatment arms using a two-sample t-test with a two-sided alternative. Linear mixed models will also be used to assess these scores longitudinally.

Patient satisfaction with trial participation by treatment arm as measured by the Was It Worth It Questionnaire at 24 months after radiation: Was It Worth It questionnaire responses to each of the five questions at 24 months will be summarized and the will be compared across treatment arms using a Chi-square tests with a two-sided alternative. In particular, for questions 1-3, the proportion of patients who answered "yes" will be compared across the two treatment arms, and for questions 4 and 5, we will compare the proportion of patients who answered "it got worse" and "worse than I expected" (respectively) across the two arms.

12.4.5 Economic Analyses

Direct costs of medical care to each patient will be estimated using utilization information from the health care expense survey and the health care utilization survey, along with publicly available Medicare reimbursement rates. In particular, based on the reported number of outpatient visits to the radiation oncologist, medical oncologist, surgeon who performed mastectomy, plastic surgeon or physical therapist, and the number of visits to the emergency room, the number of hospital admissions (and the days per each hospital admission), and the number of surgical procedures to breast reconstruction (along with the names of the procedures), Medicare reimbursement rates can be used to estimate what the direct cost to each patient would be if that patient were covered by Medicare. Generalized linear models will then be used to model these costs as a function of treatment, time on study, and all available baseline patient characteristics to assess the extent to which estimated direct cost is impacted by the type of radiation dosing. Given the well-known fact that healthcare costs are typically highly skewed, regression models will employ the appropriate distribution and transformation link. We will also assess the degree to which indirect costs differ across the two treatment arms. Specifically, using information from the phone survey, along with information on work status prior to breast cancer diagnosis, the average number of days worked per week (at baseline), and the average number of hours worked per day (at baseline), we will estimate the hours of work missed and the total distance traveled to receive radiation treatment for each patient. These two endpoints will be modeled (separately) as a function of treatment, time on study, and all available baseline patient characteristics to assess the extent to which the treatment arms differ with respect to indirect cost.

In addition to using them to estimate direct costs, the health care utilization measures (number of outpatient visits to the radiation oncologist, medical oncologist, surgeon who performed mastectomy, plastic surgeon, physical therapist; the number of visits to the emergency room, the number of hospital admissions, the days per each hospital admission, and the number of surgical procedures to breast reconstruction) will be compared (separately) across the two dosing arms. Given that these outcomes are counts, appropriate count regression models (e.g., passion regression, negative binomial regression or zero-inflated negative binomial regression) will be used to account for any residual imbalance between the study arms following randomization.

EQ-5D survey results for the baseline and follow-up will be presented in three ways: (i) the descriptive system on the 5 dimensions will reflect the patients general health profile; (ii) EQ-VAS will represent patients' self-reported health status; and (iii) the summary measure of generic health status in terms of EQ-5D-3L index value. In order to obtain the last measure, EQ-5D responses representing specific health state will be converted to a single index value using the EQ-5D-3L value sets for the U.S. This, along with the survival data, will then be used to estimate the effectiveness measure in our cost-effectiveness analysis, that is, quality adjusted life year or QALY. Mean QALYs between interventions will be compared using two-sided t-test. Cost-effectiveness will be assessed and compared in terms of incremental cost-effectiveness ratio or ICER, that is, US dollars per QALY between the interventions. Costs associated with each of the interventions will be estimated. For healthcare utilizations mentioned above, costs will be imputed from the literature. Extensive sensitivity analyses will be conducted to document sensitivity of the final results to any of the imputed cost parameters.

12.5 Correlative studies (A221505-ST1)

We expect to enroll 880 patients to the treatment portion of this study. Assuming a 10% drop-out rate, we expect to have 792 patients evaluable for the primary endpoint. We further anticipate blood samples will be available for 80% of these patients, resulting in a total sample size of 634 patients for this biomarker sub-study. Assuming the 24-month breast reconstruction complication rate is 25%. The detectable differences were computed for various minor allele frequencies with 80% power using a one-sided type I error rate of 0.0036 (= 0.05/14, a Bonferroni correction for multiple

comparisons). The power calculations were based on a chi-square test of binomial proportions and assuming that the SNPs have recessive effect on 24-month breast reconstruction complication rate. The detectable differences are shown in Table 2 for a range of minor allele frequency for the SNPs shown in Table 1. Of particular interest, the allele frequency for MDM2 rs2279744 is close to 0.4. We expect approximately 101 out of 634 patients to be homozygous for this variant. There is sufficient power at this sample size and genotype frequency to detect an increase in 24-month complication rate from 25% (in the control group) to 42.5% (in the homozygous variant group) at the 1-sided type I error of 0.0036. The other scenarios in Table 2 represent the minimum (0.2) and the maximum (0.5) MAF for the SNPs represented in Table 1.

Table 2: Detectable Difference with 80% Power

Minor Allele Frequency	Number of patients		Detectable Difference (%)
	Homozygous variant	Non-homozygous variant	
0.2	25	609	33
0.4	101	533	17.5
0.5	158	476	15

Logistic regression model will be used to access the association between each SNP and 24-month complication. The analysis will adjust for treatment arm and other baseline demographics and clinical factors as appropriate. We will also look at the frequencies separately by treatment arm as well as in both arms together (although we do not expect to see a difference in this non-inferiority study). Similar analysis will be conducted to evaluate the association between each SNP and lymphedema as well as local-regional recurrence.

12.6 Missing Data

If the proportion of missing patient information is larger than 5%, we will examine the missingness mechanism by modeling indicators of missing values as a function of baseline patient characteristics, observed patient-reported outcomes and missingness of patient-reported outcomes.

12.6.1 If as a result of this analysis, we feel it is reasonable to assume that missingness depends solely on the covariates (missing completely at random, MCAR) or depends on the covariates and observed PRO scores only (missing at random, MAR) , we will enhance the primary analysis to incorporate these covariates. [85]

12.6.2 If as a result of this analysis, we feel the missingness likely depends not only on the covariates and observed PRO scores, but also on the missing PRO score (missing not at random, MNAR), we will explore advanced models.

12.7 Study Monitoring

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

12.7.2 Adverse Event Stopping Rule

Throughout the course of the study, we will monitor adverse events in both study arms, and may suspend accrual if patients are experiencing a large number of adverse events. In particular, we will temporarily suspend accrual if at any time observed events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as possible, probable, or definite) meet the following criteria:

- If 25 or more of the first 50 treated patients (or 50% of all patients after 50 patients have been accrued) experience a grade 3 or higher CTCAE adverse event (with the exception of acute dermatitis).

- If 5 or more of the first 50 treated patients (or 10% of all patients after 50 patients have been accrued) experience a grade 4 or higher CTCAE adverse event.

It should be noted that, if unexpected adverse event profiles are observed which do not meet any of the above criteria, but are nevertheless worrisome, we may still consider temporarily suspending accrual. Also, adverse event stopping rules may be modified if during the course of the study, new information becomes available which suggests that such a modification is necessary, or if, after temporarily stopping accrual, the above rules are found to be overly conservative.

12.7.3 Accrual Monitoring Stopping Rule

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

12.8 Inclusion of Women and Minorities

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

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

The geographical region served by the Alliance has a population which includes approximately 13.5% minorities. Based on prior Alliance breast cancer studies, we expect about 10% of patients will be classified as minorities by race. Expected sizes of race by ethnicity subsets for patients randomized to this study are shown in the following table.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	5	0	0	0	5
Asian	7	0	0	0	7
Native Hawaiian or Other Pacific Islander	5	0	0	0	5
Black or African American	38	0	5	0	43
White	466	0	50	0	516
More Than One Race	5	0	5	0	10
Total	526	0	60	0	586

INTERNATIONAL PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	2	0	0	0	2
Asian	3	0	0	0	3
Native Hawaiian or Other Pacific Islander	2	0	0	0	2
Black or African American	8	0	1	0	9

White	247	0	27	0	274
More Than One Race	2	0	2	0	4
Total	264	0	30	0	294

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa.

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

13.0 CORRELATIVE AND COMPANION STUDIES

There is one correlative study, A221505-ST1, which will evaluate biological correlates of adverse radiation response. All patients are to be encouraged to participate.

13.1 Correlative Science (Alliance A221505-ST1)

13.1.1 Background

The sequencing of the human genome has led to the discovery of several million single nucleotide polymorphisms (SNPs), some of which can alter gene function and account for unique traits between individuals. SNPs in certain genes associated with cellular function, such as cell cycle control, apoptosis, and DNA repair, can have significant functional consequences with respect to cancer susceptibility and cancer biology.[88,89] Investigators at the Rutgers Cancer Institute of New Jersey have discovered a potentially important SNP at position 309 (SNP309, rs2279744; G□T) in the promoter region of *MDM2*.[90-93] This MDM2 proto-oncogene encodes a nuclear-localized E3 ubiquitin ligase. Heterozygous and homozygous polymorphisms in this location are relatively common, with homozygous mutations present in approximately 12% of normal volunteers. Experimental systems have demonstrated that cell lines homozygous for the polymorphism result in overexpression of the Mdm2 protein with subsequent attenuation of p53 activity.

The Mdm2 protein has been shown to be a key regulator of p53, and has been shown to inhibit p53 activity and promote its degradation.[90,92,93] Overexpression of the Mdm2 protein resulting in lower levels of p53 results in high rates of tumor formation in animal models. Similarly, low levels of Mdm2 result in higher rates of apoptosis and increased sensitivity to radiation. Therefore, changes in the Mdm2 protein may affect both carcinogenesis and response to therapy, as a direct result of its regulation of the p53 pathway.[90,92,93] As an example, Khor et al., recently analyzed expression of Mdm2 in a large cohort of men treated for prostate cancer on the RTOG 9202 study. On multivariate analysis in 487 patients, Mdm2 overexpression correlated with overall mortality and distant metastasis rate.[94] Similarly, Tu and colleagues sequenced both the MDM2 rs2279744 and the p53 gene (TP53) SNP; at codon 72 (rs1042522;C→G;Pro72Arg) in 189 patients with oral cavity carcinoma treated with postoperative RT.[86] They found that patients carrying the G/G variant of MDM2 rs2279744 or the Arg/Arg amino acid at codon 72 of TP53 had worse overall survival and disease-free survival than patients carrying other polymorphic variants. Interestingly, patients with both of the above variants in MDM2 and TP53 had the highest hazard ratio for mortality and poor control.

In addition to this relevance for disease control, SNP analysis may play an important role in the identification of individuals predisposed to adverse radiation reactions. Germline SNPs in MDM2 have been shown to render cells susceptible to genotoxic stresses, such as chemotherapy and radiation therapy. For example, Zheng and colleagues examined MDM2 rs2279744 and p53 rs1042522 as well as another MDM2 SNP (MDM2 c.−461C > G (rs937282, MDM2 C1797G) using PCR-based RFLP in 444 patients with advanced NSCLC treated with platinum based therapy.[95] They demonstrated a strong correlation of the MDM2 rs2279744 (G/T genotype) with severe hematologic and overall toxicity. Severe GI toxicities correlated with MDM2 rs937282 (C/G heterozygotes). The authors looked at diplotypes of MDM2 using these two SNPs and found further associations with toxicities. Thus, it is quite compelling that MDM2 rs2279744 has been implicated in both disease-related outcomes as well as normal tissue toxicity across different disease settings.

In another example, Qian and colleagues very recently reported on a cohort of 663 patients also with advanced NSCLC who had received first line platinum based chemotherapy.[96] Five tagging SNPs in MDM2 were genotyped and correlated with toxicity and disease outcomes. Two of these SNPs, rs1470383 and rs1690924, showed associations with overall/hematological and GI toxicities (respectively). As demonstrated with cisplatin based combination chemotherapy, it is quite possible that patients harboring such a SNP could potentially be more sensitive to the adverse

normal tissue effects of another DNA-damaging agent such as radiation therapy. Indeed, similar work in other candidate genes has demonstrated such an association. For example, several investigators have reported a correlation between grade 3 radiation toxicity and possession of a G→A variant at nucleotide 5557 (Asp1853Asn, rs1801516) in ATM (ATM serine/threonine kinase previously known as the ataxia-telangiectasia mutated gene).[97-100] Andreassen and colleagues analyzed DNA samples from 43 patients treated with post-mastectomy radiation therapy and found that carriers of this SNP had a lower ED50 (dose that resulted in a 50% incidence of grade 3 radiation fibrosis) in logistic regression model. Similarly, enhanced host radiosensitivity has been correlated with SNPs in TGFB1,[101,102] whose protein product is well-known and a studied regulator of cell growth, inflammation, and radiation-associated fibrosis. XRCC1, XRCC3, XRCC5, and LIG4 (DNA Ligase 4) encode proteins involved in DNA damage repair and SNPs in these genes have been correlated with radiation-related toxicity.[103-105] Similarly, Fu and colleagues examined SNPs in inflammatory genes and lymphatic growth factors and demonstrated associations between lymphedema and SNPs in interleukin genes IL4 (rs2243250, rs207087), IL6 (rs1800795), IL13 (rs1800925) and VEGFC (rs3775203), in 140 prospective studied women, as scored by measurement and a validated symptom instrument.[106] In a cohort of over 500 patients, Leung and colleagues found associations of SNPs in IL4 (rs2227284), IL10 (rs1518111) and NFKB2 (rs1056890) with development of secondary lymphedema after cancer therapy.[107] Approximately 300 of the patients had adjuvant radiation therapy. Newman and colleagues used a nested case-control design to examine candidate gene determinants of lymphedema after cancer therapy in 120 women.[108] SNPs in KDR (VEGF receptor 2, rs2239702), FLT4 (VEGF receptor 3, rs10464063), and RORC (rs12128071 and rs11801866; a member of the nuclear hormone receptors) were associated with lymphedema. SNP analysis of these and additional genes may answer some of the questions related to the heterogeneity of empirically observed differences in host response to radiation therapy.

A PMRT study of two different fractionation schedules could be an ideal background for exploring possible associations of candidate SNPs with poor radiation outcomes such as Baker 3 or 4 contracture, reconstruction loss, and lymphedema. We hypothesize that a germline homozygous G/G variant of SNP309 in MDM2 will correlate with with a higher likelihood of adverse radiation reactions in a prospectively studied cohort of women receiving hypofractionated PMRT. Additional genes in the p53 and DNA repair axes as well as candidates in inflammatory pathways that have already been reported will be evaluated for validation (Table 1). Our work may identify groups of patients who are at risk for higher rates of radiation toxicity.

Table 1
List of 14 candidate SNPs from 10 genes

Number of SNPs	Genes	dbSNP id	Chromosome	Wild type (WT) allele	Variant allele	Global Frequency	
						Variant (minor) allele	Variant genotype (%)
1	*FLT4*	rs10464063	5	C	T	0.456	20.7
2	*IL10*	rs1518111	1	C	T	0.427	18.2
3	*IL13*	rs1800925	5	C	T	0.255	6.5
4	*IL4*	rs2070874	5	C	T	0.401	16.1
5	*IL4*	rs2227284	5	T	G	0.393	15.4
6	*IL4*	rs2243250	5	T	T	0.470	22.1
7	*KDR*	rs2239702	4	C	T	0.219	4.8
8	*MDM2*	rs1690924	12	T	C	0.346	12.0
9	***MDM2***	**rs2279744**	**12**	**T**	**G**	**0.367**	**13.4**
10	*MDM2*	rs937282	12	G	C	0.497	24.7
11	*NFKB2*	rs1056890	10	G	A	0.290	8.4
12	*TGFB1*	rs1800469	19	G	A	0.368	13.5
13	*TP53*	rs1042522	17	C	G	0.457	20.9
14	*VEGFC*	rs3775203	4	G	T	0.380	14.5

This phase III trial, in which all women will have post-mastectomy radiation therapy (PMRT) and an attempted chest wall reconstruction, has a primary endpoint of reconstruction complications at 24 months. We hypothesize that a polymorphism in MDM2 (position 309 (SNP309, rs2279744; T→G)) will correlate with a higher likelihood of having a reconstruction complication. The reconstruction complication endpoint is a composite endpoint as described in Section 2.1. Events that can trigger a scorable event for the primary endpoint are listed in Section 9.2 and include:

a. Complete failure of the implant/skin flap.

b. Unplanned re-operation(s),

c. Re-operation for contracture management

d. Unplanned admission for reconstruction related issue(s) including but not limited to infection, wound healing complication or pain

The estimated background rate of having a reconstruction complication (as described) is estimated to be 25%. We believe there is compelling rationale based on existing literature to examine this particular SNP with a radiation-related endpoint, as we describe above. Secondary endpoints are also major component of this trial and include careful recording of separate toxicities such as lymphedema as well as disease control endpoints such as local-regional control.

While our primary hypothesis will examine MDM2 rs2279744 as a germline correlate of host tissue sensitivity, we believe there is also sufficient pre-existing data to attempt a validation of additional candidate SNPs as listed above. We propose to genotype patient DNA samples for candidate SNPs in MDM2 as well as in additional genes with important roles in inflammation and DNA-damage sensing and repair. We have identified a panel of candidate SNPs with strong pre-existing data to suggest a correlation with radiotherapy toxicity or with an endpoint of interest to us (such as post-therapy lymphedema).

This study represents a very unique setting to study germline biologic predictors of radiation response. Differences in how patients respond to radiotherapy are real and likely multifactorial. This trial will attempt to validate important hypotheses. Further, banking of these clinical trial specimens will allow for future evaluation of additional candidate genes of host sensitivity to radiation therapy, particularly if new associations are reported in the literature. For example, we

may learn that different genes involved in the DNA damage/repair axis such as XRCC1, XRCC3, XRCC5 and LIG4 are relevant to radiation toxicities and we will be able to probe these.

13.1.2 Objectives

- To analyze polymorphisms in MDM2 and in genes including TP53, ATM, TGFB1, IL4, IL6, and IL10 and determine correlations with a higher likelihood of adverse radiation reactions (radiation sensitivity) and with toxicities
- To analyze polymorphisms in MDM2 and in genes including TP53, ATM, TGFB1, IL4, IL6, and IL10 to determine correlations with secondary endpoints such as local-regional control.

13.1.3 Methods

Blood Sampling, DNA Isolation and Genotyping: Venipuncture will be performed to obtain 10 mL of whole blood from patients who consent to participate in this companion study. The samples will be coded with a unique study identification code. This unique study identifier will not be related to the patient's medical record number or social security number and will be unique to the study. After the sample has been coded it will be sent to the Alliance biorepository at Mayo Clinic.

DNA will be isolated from mononuclear cells utilizing a spin column method (Qiagen). DNA will be stored in eppendorf tubes labeled only with the numerical identifier in a locked -20 degree freezer at Mayo Clinic. DNA samples will be stored indefinitely.

SNP selection and Genotyping:

TagSNPs will be derived for the 10 genes implicated in this proposal namely, MDM2, FLT4, IL4, IL10, IL13, KDR, NFKB2, TGFB1,TP53, VEGFC. The derived tagSNPs will include the 14 SNPs indicated in Table 1. Genotype data from HapMap and dbSNP linked to the National Institute of Environmental Health Sciences (NIEHS) SNPs Program and to the Genome Variation Server [redacted] will be used to derive haplotype tagged SNPs for the genes above. SNPs with allele frequencies ≥ 20% and r2 ≥ 0.80 will be selected for genotyping. It is important to indicate here that there's ethnic variation in specific SNPs and frequency of SNPs, therefore genotype information from the database should reflect the patient population on the trial. For example,,tagSNPs will be derived from genotype data from both Caucasian and African-American databases.

The acquired tagSNPs will be genotyped in the Genotyping Core of the Mayo Clinic Medical Genome Facility (MGF) on either the Sequenom (now owned by Agena) or the Illumina GoldenGate custom array.

Whenever possible, if the genotyping fails in some SNPs for example, the MDM2 promoter will be analyzed for sequence variation by PCR amplification and subsequent sequencing by the DNA Synthesis and Sequencing Core Facility. PCR amplification will be carried out using DNA oligonucleotide primers. The PCR products will be cleaned using QIAquick PCR Purification kit (Qiagen). Subsequent sequencing will be performed using Applied Biosystems BigDye Terminator (v3.1) Cycle Sequencing kits, GeneAmp PCR System 9600/970 and ABI Prism 3700 DNA Analyzer (Applied Biosystems).

The Agena iPLEX (previously called sequenom) genotyping protocol involves PCR amplification of DNA using SNP specific primers, followed by a base extension reaction using the iPLEX Gold chemistry (Agena Biosciences, San Diego, CA). The protocol has been used for years and will briefly be described here. SNP-specific PCR and extension primers were designed and organized into pools with the Assay Design Suite (Agena). All primers were purchased from Integrated DNA Technologies (Coralville, IA). A QC run was performed with Coriell and CEPH controls, and results were tested for Mendelian inconsistencies. HotStar Taq Polymerase (Qiagen) was used for all PCRs. 15 ng of DNA was added to each 5-ul PCR reaction mixture in a 384-well microtiter plate. The PCR condition was 94°C for 15 min for hot start, followed by 45 cycles of denaturing at

94°C for 20 sec, annealing at 56°C for 30 sec, extension at 72°C for 1 min for 45 cycles, and final incubation at 72°C for 3 min. The PCR products were then treated with SAP (shrimp alkaline phosphatase, Agena) for 40 min at 37°C then ramped to 85°C for 5 min to remove excess dNTPs. The final base extension products were diluted in double distilled water and then treated with 6mg of SpectroCLEAN (Agena) resin per well to remove contaminating salts. 10-18 nl of treated extension product was spotted to the appropriate location on a 384-pad SpectroCHIP II (Agena) using a RS1000 Nanodispenser (Agena, San Diego, CA). A MassARRAY Analyzer Compact MALDI-TOF MS (Agena) was used for data acquisitions from the SpectroCHIP. All resultant genotyping calls were performed in real time by the MassARRAY Typer Analyzer v4.0.26.73 (Agena).

13.1.4 Statistical Analyses

The statistical analysis for this sub-study is described in Section 12.5 of the protocol.

14.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING

14.1 Radiation Therapy Credentialing

IROC Institutional Requirements

There are no specific credentialing requirements for those using 3D conformal planning on this study. Institutions using IMRT must be credentialed prior to delivery of radiation therapy on any protocol patient. Credentialing requirements are listed in the table below. Institutions previously credentialed for use of IMRT in clinical trials need not repeat the credentialing for this trial.

Web Link for Credentialing Procedures and Instructions: [redacted]

	Treatment Modality		
RT Credentialing Requirements	**3D**	**IMRT**	**Key Information**
Facility Questionnaire		X	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email [redacted] to receive your FQ link.
Credentialing Status Inquiry Form		X	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website [redacted]
Phantom Irradiation		X	The IMRT head and neck phantom provided by the IROC Houston QA Center must be successfully irradiated. Instructions for requesting and irradiating the phantom may be found on the IROC Houston website [redacted] Tomotherapy and Cyberknife treatment delivery modalities must be credentialed individually.
Institution			Institutions will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and Alliance Headquarters that all desired credentialing requirements have been met.

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16.0 MODEL CONSENT FORM

Study Title for Study Participants: Randomized trial testing the safety and patient experience of short course radiation after mastectomy and breast reconstruction for breast cancer

Official Study Title for Internet Search on [redacted]
Alliance A221505: RT CHARM: Phase III Randomized Trial of Hypofractionated Post Mastectomy Radiation with Breast Reconstruction

This study is conducted by the Alliance for Clinical Trials in Oncology, a national clinical research group supported by the National Cancer Institute. The Alliance is made up of cancer doctors, health professionals, and laboratory researchers, whose goal is to develop better treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of cancer patients.

What is the usual approach to my radiation after mastectomy (surgery to remove the entire breast)?

You are being asked to take part in this study because you have been diagnosed with breast cancer and your doctor has recommended that you receive radiation therapy after your mastectomy to prevent your breast cancer from coming back. Radiation uses particles of energy to kill any remaining cancer cells where your breast was removed or in the lymph nodes. Radiation after mastectomy has been shown to reduce the number of patients whose breast cancer returns. Women with cancer in their lymph nodes after mastectomy have been shown to live longer when they receive radiation therapy. Radiation treatments are given daily, Monday through Friday, to breast cancer patients over a treatment course of 5 to 6 weeks.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to receive standard radiation treatment as described above, without taking part in a study
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated with radiation

Why is this study being done?

You are being asked to take part in this study so that we can determine whether a short-course radiation therapy option (3 to 4 weeks) after mastectomy is as safe and effective in the setting of breast reconstruction as the usual 5 to 6 week treatment course. Short-course radiation therapy is also called hypofractionated radiation. This study will also examine whether a shorter course of radiation therapy will lower treatment costs and improve patient satisfaction.

There will be about 880 people participating in the study.

What are the study groups?

All patients enrolled on this trial will receive radiation after mastectomy. All patients will also have breast reconstruction. The reconstruction can be done at the time of the mastectomy before you enroll to the study, or as a separate surgery later.

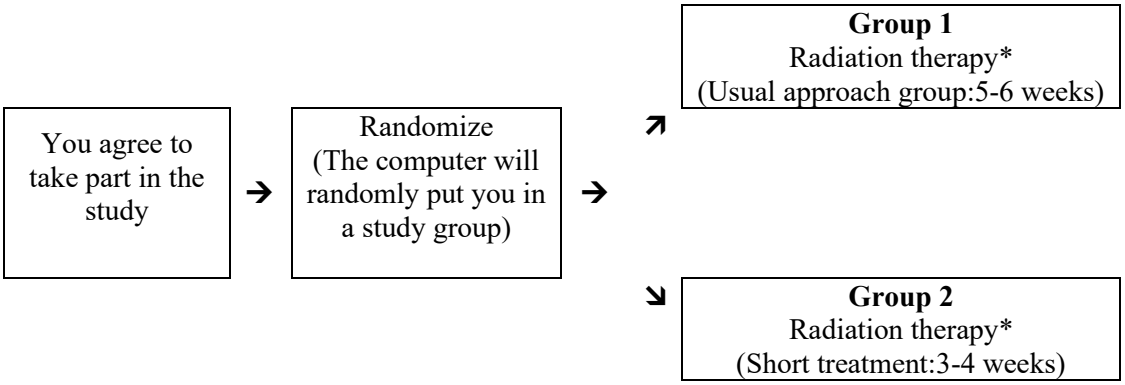
This study has two study groups:

- Group 1 will get the usual 5 to 6 weeks radiation therapy used for this type of cancer.
- Group 2 will get a shortened course with 3 to 4 weeks radiation therapy for this type of cancer.

Radiation in the two treatment groups will be slightly different, as a smaller total radiation dose is necessary when the radiation is given in a shorter period of time. However the effective dose of radiation on the cancer and your body, is thought to be about the same in both treatment groups.

A computer will by chance assign you to one of the two treatment groups being evaluated in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the others.

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



* Breast reconstruction may happen before or after radiation as predetermined by your surgeon.

You will be assessed during and after completing radiation, similar to usual care. You will be asked to come to the clinic between 2 and 8 weeks after the end of your radiation therapy, then at 6, 12, 18, 24 and 30 months following radiation, and then annually from 3 years to 5 years after completing radiation.

Your doctor may recommend chemotherapy drugs or anti-estrogen medications that are commonly used before or after radiation therapy.

How long will I be in this study?

You will receive the radiation therapy for either 3 to 4 weeks or 5 to 6 weeks. After you finish your radiation treatment, your doctor will continue to watch you for side effects and follow your condition for 5 years after you have completed radiation therapy.

Ten and fifteen years after completing radiation, your study doctor may review your medical records to confirm that no breast cancer recurrence or complications have occurred since your 5 year visit. No clinic visit will be required at these 10 and 15 year assessments.

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

Before you begin the study, your doctor will review the results of your exams, tests and procedures to make sure it is safe for you to take part. If you join the study, there will be exams, tests, and procedures that will be done to closely monitor your safety and health. All of these are included in the usual care you would receive even if you were not in a study.

In addition:
After enrolling in the study, you will complete questionnaires and arm measurements. You will be asked questions about lymphedema (swelling), physical, psychosocial and sexual well-being, as well as satisfaction with your breast/nipples/abdomen, and general overall satisfaction with your breast reconstruction and cancer care. In addition, you will be given a short questionnaire about the general state of your health. These questionnaires should take about 30 to 45 minutes to complete. In addition, a nurse will take several physical measurements on you. Each arm will be measured for swelling. This measurement will take about 30 minutes.

Photographs of your reconstructed breast and your non-radiation breast (which may also be reconstructed) will be taken for comparison. Your face will not be captured on these photographs. These photographs will not include your name or other personal information and will be saved in the Alliance database.

Two to eight weeks after completing radiation, you will be asked to complete a survey about the costs related to your radiation treatment, including child care, travel, and time away from home. You will also be asked the distances you travel from home, work and your treatment clinic. To help you remember these costs, we will give you a diary to be filled out weekly during radiation therapy and ask that you use it when you complete the survey. The survey will take about twenty minutes and you will be asked to bring it to your first follow up visit after radiation treatment.

Six months after completing radiation, you will be asked questions about arm swelling (5 to 10 minutes) and have arm measurements taken (about 30 minutes). In addition, you will be given a short, 5-minute questionnaire about the general state of your health.

One year after radiation is done, you will receive another survey to report the approximate number of medical visits you had during your entire course of treatment (surgery, radiation and reconstruction). We will ask you to continue to fill out the diary to help with remembering the number of visits you have made during the year. These surveys will be used to help determine the overall costs related to your

radiation therapy. At this time your study doctor will send the billing codes related to your treatment to the researchers if you receive treatment in the United States.
In addition, you will be given the short, 5-minute questionnaire about the general state of your health **one year after radiation is done**, and then again **18 months after radiation** is done.

Two years after completing radiation, you will be asked to complete the questionnaires about your physical, psychosocial and sexual well-being, as well as satisfaction with your breast/nipples/abdomen, and general overall satisfaction with your breast reconstruction and cancer care. These questionnaires should take about 30 to 45 minutes to complete. You will be also asked questions about lymphedema (5 to 10 minutes) and have arm measurements of swelling (about 30 minutes). Lastly, we will ask to repeat taking the photographs of your reconstructed breast and your non-radiation breast. Finally, you will be given the short, 5-minute questionnaire about the general state of your health.

Five years after completing radiation, you will be asked one more time to complete the questionnaires that you completed at 2 years (described above). You will not need to have arm measurements of swelling done at this time.

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

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- If you receive treatment in the United States, the billing codes related to treatments you receive for up to 12 months after your radiation treatment will be sent to the researchers. This may include sensitive information not related to your cancer treatment that you may have received (for example, your mental health visits, or substance abuse treatment).
- The radiation therapy approach may not be better, and could possibly be worse, than the usual approach for your cancer.

There is also a risk that you could have side effects from the radiation therapy. Studies in women treated with breast conserving surgery show that women have experienced equal to improved breast appearance, skin redness and long term arm swelling with short course radiation schedules. In both treatment arms, short term radiation side effects may start a week or two into your radiation treatment and should resolve within 2-8 weeks after completing radiation. It is possible that short course radiation could increase the risk of injury to the heart, nerve of the arm (brachial plexus) as well as the risk of arm swelling.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.

- The study doctor may be able to treat some side effects.
- The study doctor may give you short radiation treatment breaks to try to reduce side effects.

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

Possible Side Effects of Radiation Therapy
These estimates above are based on standard fractionation radiation. The number of people with side effects may be higher or lower with hypofractionated radiation therapy.

COMMON, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, more than 20 and up to 100 may have:
• Change in the shape and size of the reconstructed breast • Reddening, tanning, or peeling of the skin • Mild pain • Temporary Hair loss under the arm • Tiredness • Scarring in the lungs seen on X-Ray, not causing any breathing change • Thickening and numbness of the skin, or tightening of the chest wall

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, from 4 to 20 may have:
• Permanent swelling of the chest wall and arm • Shoulder stiffness • Decreased thyroid function • Rib fracture • Reconstruction complications (wound healing, infection, etc.)

RARE, AND SERIOUS In 100 people receiving radiation therapy, 3 or fewer may have:
• Heart injury • Lung fibrosis/scarring causing breathing difficulties • Damage to the nerve supplying sensation and strength to the arm. • Secondary radiation induced cancers • Sores or ulcers on the skin or near the cancer location • Bleeding from the skin

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant or breastfeed while in this study. The radiation therapy used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study. You should tell your doctor immediately if you think that you are pregnant.

Breast reconstruction and radiation after mastectomy both carry a risk of side effects and complications even without participation in this study.

Possible Side Effects of Reconstruction, with or without being on this study:

- After operation infection
- Wound healing difficulties
- Pain
- Tightening around the breast implant which could cause pain, an undesirable cosmetic appearance, or the need for additional surgeries
- Failure of the implant/skin flap to heal properly that may result in its removal. Failure is usually from infection or wound healing difficulties.
- Additional hospital admission(s)
- Unplanned re-operation(s)

It is possible that short course, hypofractionated, radiation may increase the frequency and severity of any of the above side effects.

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the study approach is better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study. It is strongly advised to not stop participation during your radiation. If you choose to stop during your radiation treatment, your study doctor may change your radiation schedule.

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

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor or IRB

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

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

What are the costs of taking part in this study?

Your Potential Costs:
You and/or your health plan/insurance company will be responsible for:

- The costs of treating your cancer, non-study drugs and all premedications, fluids and procedures.
- Exams, tests, and procedures that may be needed to manage side effects and to monitor your safety.

You are responsible for all co-pays and deductibles according to your insurance plan including costs associated with radiation and breast reconstruction.

It is important for you to speak to your insurance plan to ensure that you understand your coverage and whether you might need approval to take part in a study. While most plans cover clinical trials, it is your responsibility to check with them.

Ask your doctor, nurse, case manager, or financial advisor if you are unsure which costs will be billed to your insurance plan. If you have other questions about what your plan covers, you may also ask to speak to a financial advisor or case manager at the hospital or clinic.

You will not be paid for taking part in this study. If the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

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

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

Your face will not be captured on the photographs of your reconstructed breast and your non-radiation breast. These photographs will not include your name or other personal information and will be saved in the Alliance database.
There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor, Alliance for Clinical Trials in Oncology.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

The Alliance has received a Certificate of Confidentiality from the federal government, which will help us to protect your privacy. The Certificate protects against the involuntary release of information about you collected during the course of the study. The researchers involved in this project may not be forced to identify you in any legal proceedings (criminal, civil, administrative, or legislative) at the federal, state or local level. However, some information may be required by the Federal Food, Drug, and Cosmetic Act, the U.S. Department of Health and Human Services, or for purposes of program review or audit. Also, you may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests the release of information about you in writing (through, for example, a written request to release medical records to an insurance company), the Certificate does not protect against that voluntary disclosure.

Where can I get more information?

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

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

Who can answer my questions about this study?

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

ADDITIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say "no" to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional Sample Collection for Laboratory Studies and Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about how genes affect health and disease and how people respond to treatment. Genes carry information about features that are found in you and your family, from the color of your eyes to health conditions for which you may be at risk. Research that studies your genes is known as genomics or genetics.

If you choose to take part in this study, the study doctor for the main study would like to collect *2* teaspoons of blood for research on how your body responds to radiation therapy.

In addition, researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by the Alliance and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) About 2 teaspoons of blood will be collected from a vein in your arm.
2) Your baseline blood sample and some related health information will be sent to a researcher for use in the study described above. Remaining baseline blood samples may be stored in the

Biobank, along with samples from other people who take part. The samples will be kept until they are used up.

3) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the Alliance, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
4) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your baseline blood samples.
5) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.
6) Your specimens will be labeled with your initials and the dates that they were taken. They will be sent to the lab at the Alliance Biobank.

WHAT ARE THE POSSIBLE RISKS?

1) The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your samples are sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and Alliance staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom the Alliance sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option:

SAMPLES FOR THE LABORATORY STUDIES:

1. I agree to have my specimen collected and I agree that my specimen samples and related information may be used for the laboratory study described above.

   YES NO

SAMPLES FOR FUTURE RESEARCH STUDIES:

2. My samples and related information may be kept in a Biobank for use in future health research.

   YES NO

3. I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

   YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

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

Participant's signature_____

Date of signature_____

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____

APPENDIX I: PATIENT INFORMATION SHEETS

Patient Information Sheet

Patient Completed Booklet A (Pre-reconstruction)
Prior to Radiation Therapy; for patients who have not yet completed reconstruction

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You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' 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.

1. This booklet contains the following:
    a. Breast-Q survey (Mastectomy Postoperative Module)
    b. Lymphedema and Breast Cancer Questionnaire (LBCQ)
    c. EQ-5D-3L

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

3. Complete the booklet and return it to the research coordinator today or bring the booklet with you to your next clinical visit.

4. It is very important that you return the booklet to us, whether you finish the study or not.

5. You will be given the research coordinator's name and telephone number. You can call any time with any concerns or questions.

Thank you for taking the time to help us with this study.

Patient Information Sheet

Patient Completed Booklet A (Post-reconstruction)
Prior to Radiation Therapy; For patients who have completed reconstruction

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You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' 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.

1. This booklet contains the following:
    a. Breast-Q survey (Reconstruction Postoperative Module)
    b. Breast Lymphedema Symptom Survey (BLE)
    c. Lymphedema and Breast Cancer Questionnaire (LBCQ)
    d. EQ-5D-3L

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

3. Complete the booklet and return it to the research coordinator today or bring the booklet with you to your next clinical visit.

4. It is very important that you return the booklet to us, whether you finish the study or not.

5. You will be given the research coordinator's name and telephone number. You can call any time with any concerns or questions.

Thank you for taking the time to help us with this study.

Patient Information Sheet

Patient Completed Booklet B
6 months after the End of Radiation Therapy

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' 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.

1. This booklet contains the following:
    a. Breast Lymphedema Symptom Survey (BLE)
    b. Lymphedema and Breast Cancer Questionnaire (LBCQ)
    c. EQ-5D-3L

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

3. Complete the booklet and return it to the research coordinator today or bring the booklet with you to your next clinical visit.

4. It is very important that you return the booklet to us, whether you finish the study or not.

5. You will be given the research coordinator's name and telephone number. You can call any time with any concerns or questions.

Thank you for taking the time to help us with this study.

Patient Information Sheet

Patient Completed Booklet C
12 and 18 months after the End of Radiation Therapy

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' 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.

1. This booklet contains the following:
    a. EQ-5D-3L

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

3. Complete the booklet and return it to the research coordinator today.

4. It is very important that you return the booklet to us, whether you finish the study or not.

5. You will be given the research coordinator's name and telephone number. You can call any time with any concerns or questions.

Thank you for taking the time to help us with this study.

Patient Completed Booklet D
2 Years after the End of Radiation Therapy

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' 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.

1. This booklet contains the following:
    a. Breast-Q survey (Reconstruction Postoperative Module)
    b. Breast Lymphedema Symptom Survey (BLE)
    c. Lymphedema and Breast Cancer Questionnaire (LBCQ)
    d. EQ-5D-3L
    e. Was it Worth it (WIWI) Questionnaire

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

3. Complete the booklet and return it to the research coordinator today.

4. It is very important that you return the booklet to us, whether you finish the study or not.

5. You will be given the research coordinator's name and telephone number. You can call any time with any concerns or questions.

Thank you for taking the time to help us with this study.

Patient Information Sheet

Patient Completed Booklet E
(5 years after the End of Radiation Therapy)

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' 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.

1. This booklet contains the following:
    a. Breast-Q survey (Reconstruction Postoperative Module)
    b. Breast Lymphedema Symptom Survey (BLE)
    c. Lymphedema and Breast Cancer Questionnaire (LBCQ)

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

3. Complete the booklet and return it to the research coordinator today.

4. It is very important that you return the booklet to us, whether you finish the study or not.

5. You will be given the research coordinator's name and telephone number. You can call any time with any concerns or questions.

Thank you for taking the time to help us with this study.

Patient Information Sheet

Patient Completed Booklet F
2-8 Weeks after the End of Radiation Therapy

You have been given a booklet to complete for this study. The booklet contains some questions about your health care expenses as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the cost of your care.

1. This booklet contains the following:
    a. Patient Health Care Expense Diary (To be completed from the time of starting radiation therapy until 2 to 8 weeks after completing radiation therapy)
    b. Health Care Expense Questionnaire (To be completed 2-8 weeks after radiation therapy)

2. Bring the booklet with you to your 2-8 week clinical follow-up visit. You will use the Health Care Expense Diary to help you complete the Health Care Expense Questionnaire to report expenses you incurred during this time.

3. You will be given the research coordinator's name and telephone number. You can call any time with any concerns or questions.

Thank you for taking the time to help us with this study.

Patient Information Sheet

Patient Completed Booklet G
2-8 Weeks and 12 months after the End of Radiation Therapy

You have been given a booklet to complete for this study. The booklet contains some questions about your health care expenses as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the cost of your care.

1. This booklet contains the following:
    a. Health Care Utilization Diary (Starting from the time of completing radiation therapy and to be returned to the clinic at the 12-month post-radiation therapy visit)

2. Bring the booklet with you to your 12-month clinical visit. You will use the Health Care Utilization Diary to help you report the health care services you used during this time.

3. You will be given the research coordinator's name and telephone number. You can call any time with any concerns or questions.

Thank you for taking the time to help us with this study

APPENDIX II: BREAST Q MASTECTOMY AND RECONSTRUCTION (POSTOPERATIVE) MODULES

BREAST-Q ™ MASTECTOMY MODULE (POSTOPERATIVE) 2.0 SATISFACTION WITH BREASTS

After reading each question, please circle the number in the box that best describes your situation. If you are unsure how to answer a question, choose the answer that comes closest to how you feel. Please answer all questions.

1. With your breast area in mind, in the past week, 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. How comfortably your bras fit?	**1**	**2**	**3**	**4**
c. Being able to wear clothing that is more fitted?	**1**	**2**	**3**	**4**
d. How you look in the mirror unclothed?	**1**	**2**	**3**	**4**

BREAST-Q™ - MASTECTOMY MODULE (POSTOPERATIVE) 2.0 PSYCHOSOCIAL WELL-BEING

2. With your breast area in mind, in the past week, how often have you felt:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Confident in a social setting?	**1**	**2**	**3**	**4**	**5**
b. Emotionally able to do the things that you want to do?	**1**	**2**	**3**	**4**	**5**
c. Emotionally healthy?	**1**	**2**	**3**	**4**	**5**
d. Of equal worth to other women?	**1**	**2**	**3**	**4**	**5**
e. Self-confident?	**1**	**2**	**3**	**4**	**5**
f. Feminine in your clothes?	**1**	**2**	**3**	**4**	**5**
g. Accepting of your body?	**1**	**2**	**3**	**4**	**5**
h. Normal?	**1**	**2**	**3**	**4**	**5**
i. Like other women?	**1**	**2**	**3**	**4**	**5**
j. Attractive?	**1**	**2**	**3**	**4**	**5**

BREAST-Q™ - MASTECTOMY MODULE (POSTOPERATIVE) 2.0 PHYSICAL WELL-BEING: CHEST

3. In the past week, how often have you experienced:

	None of the time	Some of the time	All of the time
a. Pain in the muscles of your chest?	**1**	**2**	**3**
b. Difficulty lifting or moving your arms?	**1**	**2**	**3**
c. Difficulty sleeping because of discomfort in your breast area?	**1**	**2**	**3**
d. Tightness in your breast area?	**1**	**2**	**3**
e. Pulling in your breast area?	**1**	**2**	**3**
f. Nagging feeling in your breast area?	**1**	**2**	**3**
g. Tenderness in your breast area?	**1**	**2**	**3**
h. Sharp pains in your breast area?	**1**	**2**	**3**
i. Aching feeling in your breast area?	**1**	**2**	**3**
j. Throbbing feeling in your breast area?	**1**	**2**	**3**
k. Swelling of the arm (lymphedema) on the side(s) that you had your breast surgery?	**1**	**2**	**3**

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BREAST-Q™ - MASTECTOMY MODULE (POSTOPERATIVE) 2.0 SEXUAL WELL-BEING

The following questions ask about your sexual well-being. If you are uncomfortable answering these questions or do not feel that they apply to you, please check the box and skip the questions that follow.☐

4. Thinking of your sexuality, how often do you generally feel:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Sexually attractive in your clothes?	**1**	**2**	**3**	**4**	**5**
b. Comfortable/at ease during sexual activity?	**1**	**2**	**3**	**4**	**5**
c. Confident sexually?	**1**	**2**	**3**	**4**	**5**
d. Satisfied with your sex-life?	**1**	**2**	**3**	**4**	**5**
e. Confident sexually about how your breast area looks when unclothed?	**1**	**2**	**3**	**4**	**5**
f. Sexually attractive when unclothed?	**1**	**2**	**3**	**4**	**5**

Please check that you have answered all the questions.

BREAST-Q™ - RECONSTRUCTION MODULE (POSTOPERATIVE) 2.0 SATISFACTION WITH BREASTS

After reading each question, please circle the number in the box that best describes your situation. If you are unsure how to answer a question, choose the answer that comes closest to how you feel. Please answer all questions.

1. If you have had a mastectomy and reconstruction of both breasts, answer these questions thinking of the breast you are least satisfied with. With your breasts in mind, in the past week, 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 reconstructed breast(s) when you are wearing a bra?	**1**	**2**	**3**	**4**
c. How normal you feel in your clothes?	**1**	**2**	**3**	**4**
d. The size of your reconstructed breast(s)?	**1**	**2**	**3**	**4**
e. Being able to wear clothing that is more fitted?	**1**	**2**	**3**	**4**
f. How your breasts are lined up in relation to each other?	**1**	**2**	**3**	**4**
g. How comfortably your bras fit?	**1**	**2**	**3**	**4**
h. The softness of your reconstructed breast(s)?	**1**	**2**	**3**	**4**
i. How equal in size your breasts are to each other?	**1**	**2**	**3**	**4**
j. How natural your reconstructed breast(s) looks?	**1**	**2**	**3**	**4**
k. How naturally your reconstructed breast(s) sits/hangs?	**1**	**2**	**3**	**4**
l. How your reconstructed breast(s) feels to touch?	**1**	**2**	**3**	**4**
m. How much your reconstructed breast(s) feels like a natural part of your body?	**1**	**2**	**3**	**4**
n. How closely matched (similar) your breasts are to each other?	**1**	**2**	**3**	**4**
o. How you look in the mirror unclothed?	**1**	**2**	**3**	**4**

 Please check that you have answered all the questions before going on to the next page

BREAST-Q™ - RECONSTRUCTION MODULE (POSTOPERATIVE) 2.0 SATISFACTION WITH IMPLANTS

2. If you have implants in both breasts, answer these questions thinking of the breast you are least satisfied with. If you do not have implants, please check the box and skip the questions that follow. ☐
   In the past week, how satisfied or dissatisfied have you been with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. The amount of rippling (wrinkling) of your implant(s) that you can see?	**1**	**2**	**3**	**4**
b. The amount of rippling (wrinkling) of your implant(s) that you can feel?	**1**	**2**	**3**	**4**

BREAST-Q™ - RECONSTRUCTION MODULE (POSTOPERATIVE) 2.0 PSYCHOSOCIAL WELL-BEING

3. With your breasts in mind, in the past week, how often have you felt:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Confident in a social setting?	**1**	**2**	**3**	**4**	**5**
b. Emotionally able to do the things that you want to do?	**1**	**2**	**3**	**4**	**5**
c. Emotionally healthy?	**1**	**2**	**3**	**4**	**5**
d. Of equal worth to other women?	**1**	**2**	**3**	**4**	**5**
e. Self-confident?	**1**	**2**	**3**	**4**	**5**
f. Feminine in your clothes?	**1**	**2**	**3**	**4**	**5**
g. Accepting of your body?	**1**	**2**	**3**	**4**	**5**
h. Normal?	**1**	**2**	**3**	**4**	**5**
i. Like other women?	**1**	**2**	**3**	**4**	**5**
j. Attractive?	**1**	**2**	**3**	**4**	**5**

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BREAST-Q™ - RECONSTRUCTION MODULE (POSTOPERATIVE) 2.0 PHYSICAL WELL-BEING: CHEST

4. In the past week, how often have you experienced:

	None of the time	Some of the time	All of the time
l. Pain in the muscles of your chest?	**1**	**2**	**3**
m. Difficulty lifting or moving your arms?	**1**	**2**	**3**
n. Difficulty sleeping because of discomfort in your breast area?	**1**	**2**	**3**
o. Tightness in your breast area?	**1**	**2**	**3**
p. Pulling in your breast area?	**1**	**2**	**3**
q. Nagging feeling in your breast area?	**1**	**2**	**3**
r. Tenderness in your breast area?	**1**	**2**	**3**
s. Sharp pains in your breast area?	**1**	**2**	**3**
t. Aching feeling in your breast area?	**1**	**2**	**3**
u. Throbbing feeling in your breast area?	**1**	**2**	**3**
v. Swelling of the arm (lymphedema) on the side(s) that you had your breast surgery?	**1**	**2**	**3**

BREAST-Q™ - RECONSTRUCTION MODULE (POSTOPERATIVE) 2.0 PHYSICAL WELL-BEING: ABDOMEN

5. The following questions are about reconstruction using a TRAM or DIEP flap (i.e., reconstruction using skin and fat from your abdomen/tummy area). If you have not had reconstruction using a TRAM or DIEP flap, please check the box and skip the questions that follow.☐

In the past week, with your abdomen (tummy area) in mind, 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. Difficulty sitting up because of abdominal muscle weakness (e.g. getting out of bed)?	**1**	**2**	**3**	**4**	**5**
b. Difficulty doing everyday activities because of abdominal muscle weakness (e.g. making your bed)?	**1**	**2**	**3**	**4**	**5**
c. Abdominal discomfort?	**1**	**2**	**3**	**4**	**5**
d. Abdominal bloating?	**1**	**2**	**3**	**4**	**5**
e. Abdominal bulging?	**1**	**2**	**3**	**4**	**5**
f. Tightness in your abdomen?	**1**	**2**	**3**	**4**	**5**
g. Pulling in your abdomen?	**1**	**2**	**3**	**4**	**5**

BREAST-Q™ - RECONSTRUCTION MODULE (POSTOPERATIVE) 2.0 SATISFACTION WITH ABDOMEN

Page 6 of 8

6. The following questions are about reconstruction using a TRAM or DIEP flap (i.e., reconstruction using skin and fat from your abdomen/tummy area). If you have not had reconstruction using a TRAM or DIEP flap, please check the box and skip the questions that follow.☐

In the past week, how satisfied or dissatisfied have you been with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. How your abdomen (tummy area) looks when unclothed?	**1**	**2**	**3**	**4**
b. The position of your navel (belly button)?	**1**	**2**	**3**	**4**
c. How your abdominal scars look?	**1**	**2**	**3**	**4**

BREAST-Q™ - RECONSTRUCTION MODULE (POSTOPERATIVE) 2.0 SATISFACTION WITH NIPPLE RECONSTRUCTION

7. If you have not had nipple reconstruction, please check the box and skip the question that follows. ☐

In the past week, how satisfied or dissatisfied are you with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
How natural your reconstructed nipple(s) look?	**1**	**2**	**3**	**4**

BREAST-Q™ - RECONSTRUCTION MODULE (POSTOPERATIVE) 2.0 SEXUAL WELL-BEING

8. The following questions ask about your sexual well-being. If you are uncomfortable answering these questions or do not feel that they apply to you, please check the box and skip the questions that follow. ☐

Thinking of your sexuality, how often do you generally feel:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Sexually attractive in your clothes?	**1**	**2**	**3**	**4**	**5**
b. Comfortable/at ease during sexual activity?	**1**	**2**	**3**	**4**	**5**
c. Confident sexually?	**1**	**2**	**3**	**4**	**5**
d. Satisfied with your sex-life?	**1**	**2**	**3**	**4**	**5**
e. Confident sexually about how your breast(s) look when unclothed?	**1**	**2**	**3**	**4**	**5**
f. Sexually attractive when unclothed?	**1**	**2**	**3**	**4**	**5**

Please check that you have answered all the questions.

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APPENDIX III: PATIENT COMPLETED LYMPHEDEMA MEASURES

Lymphedema and Breast Cancer Questionnaire (LBCQ)-Baseline and 6-month visit

Answer all questions you understand. Do not answer questions that have any words you do not understand. Circle any words you do not know. Lymphedema means swelling of the arm, hand, shoulder or upper body on the side where your cancer was found. Today means today or in the past 30 days.

Do you have limited movement of your . . .	**Today** **If yes, please describe**	**During Past 6 months** **If yes, please describe**
1. Shoulder?	No ☐ Yes ☐	No ☐ Yes ☐
2. Elbow?	No ☐ Yes ☐	No ☐ Yes ☐
3. Wrist?	No ☐ Yes ☐	No ☐ Yes ☐
4. Fingers?	No ☐ Yes ☐	No ☐ Yes ☐
5. Does your arm or hand feel weak?	No ☐ Yes ☐	No ☐ Yes ☐

The following questions pertain to arm, breast, and chest symptoms.

Have you experienced:	**Today**	**During Past 6 months**	**What action you did for this symptom: Please describe**
6. Tenderness?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
7. Swelling?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:

8. Swelling with pitting? (Pitting is when you press firmly on your skin and the dent stays long enough to feel it when you slide the pad of your finger across it.)	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
9. Redness?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
10. Blistering?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
11. Firmness/tightness?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
12. Increased temperature in your arm?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
13. Heaviness?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
14. Numbness?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
15. Stiffness?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
16. Aching?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
17. Chest wall swelling?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:

18. Chest wall or reconstructed breast swelling? (N/A if no breast)	No ☐ Yes ☐ n/a ☐	No ☐ Yes ☐ n/a ☐	No action ☐ Action:
19. Pocket of fluid develop?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action (for example, how many times drained):
20. Other Symptoms?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:

Lymphedema and Breast Cancer Questionnaire (LBCQ)-2 year and 5 year visit

Answer all questions you understand. Do not answer questions that have any words you do not understand. Circle any words you do not know. Lymphedema means swelling of the arm, hand, shoulder or upper body on the side where your cancer was found. Now means today or in the past 30 days.

Do you have limited movement of your . . .	**Now** **If yes, please describe**	**During the Past Year** **If yes, please describe**
1. Shoulder?	No ☐ Yes ☐	No ☐ Yes ☐
2. Elbow?	No ☐ Yes ☐	No ☐ Yes ☐
3. Wrist?	No ☐ Yes ☐	No ☐ Yes ☐
4. Fingers?	No ☐ Yes ☐	No ☐ Yes ☐
5. Does your arm or hand feel weak?	No ☐ Yes ☐	No ☐ Yes ☐

The following questions pertain to arm, breast, and chest symptoms.

Have you experienced:	**Now**	**During the Past Year**	**What action you did for this symptom: Please describe**
6. Tenderness?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
7. Swelling?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:

8. Swelling with pitting? (Pitting is when you press firmly on your skin and the dent stays long enough to feel it when you slide the pad of your finger across it.)	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
9. Redness?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
10. Blistering?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
11. Firmness/tightness?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
12. Increased temperature in your arm?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
13. Heaviness?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
14. Numbness?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
15. Stiffness?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
16. Aching?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:
17. Chest wall swelling?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:

18. Chest wall or reconstructed breast swelling? (N/A if no breast)	No ☐ Yes ☐ n/a ☐	No ☐ Yes ☐ n/a ☐	No action ☐ Action:
19. Pocket of fluid develop?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action (for example, how many times drained):
20. Other Symptoms?	No ☐ Yes ☐	No ☐ Yes ☐	No action ☐ Action:

Breast Lymphedema (BLE) Symptom Survey

Please answer the following questions regarding symptoms you have had within the last seven days in the operated breast.

1. Does your reconstructed breast or chest wall appear or feel swollen?

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

How much does it bother you?

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

2. Does your reconstructed breast or chest wall feel heavy?

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

How much does it bother you?

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

3. Is your reconstructed breast or chest wall redder in color?

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

How much does it bother you?

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 reconstructed breast or chest wall?

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

How much does it bother you?

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

5. Do you have axillary (armpit) fullness or numbness?

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

How much does it bother you?

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

APPENDIX IV: ARM CIRCUMFERENCE MEASUREMENTS

Reporting Period: *(check one)*

☐ Prior to radiation

☐ 6 month follow-up visit

☐ 24 month follow-up visit

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

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

☐Patient refusal

☐Site staff forgot to perform

☐Other, specify _____

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

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

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

Height __ __ . __ cm

Weight: __ __ __.__ __ kg

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

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

If Yes, treatment/interventions for arm lymphedema:

Exercises ☐Yes ☐No

Compression garment ☐Yes ☐No

Lymphatic massage ☐Yes ☐No

Benzopyrones ☐Yes ☐No

Skin care ☐Yes ☐No

☐Other, specify _____

Body Diagram *(Page 2 of 2)*

INSTRUCTIONS:

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

RIGHT

Halfway point *

Distance above antecubital fossa: __ __.__ cm

Distance below antecubital fossa: __ __.__ cm

Circumference

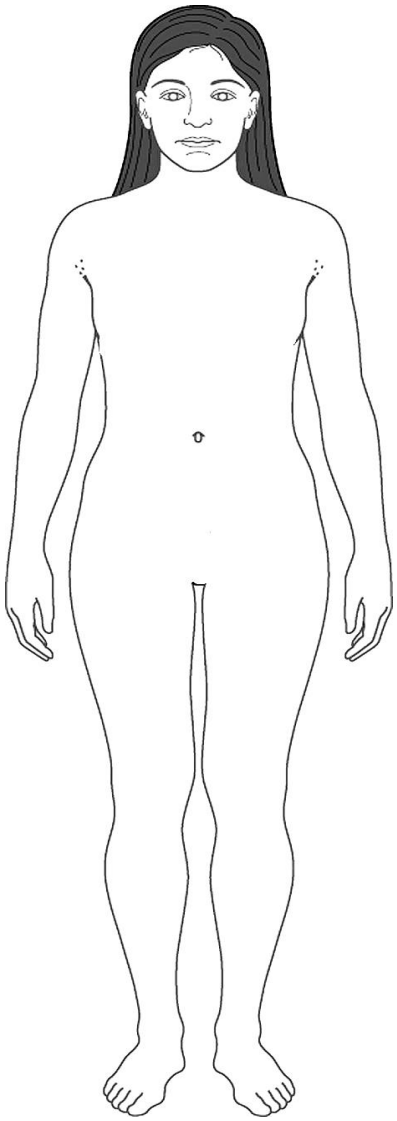
Axilla: __ __.__ cm

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

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

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

Wrist: . cm



LEFT

Halfway point *

Distance above antecubital fossa: __ __.__ cm

Distance below antecubital fossa: __ __.__ cm

Circumference

Axilla: __ __.__ cm

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

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

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

Wrist: __ __.__ cm

APPENDIX V: WAS IT WORTH IT (WIWI) QUESTIONNAIRE

Participating in a clinical trial / research study is a personal choice and an individual experience. We would like to get your feedback on your experience in this research study.

Directions: Please answer each question by circling Y (for yes), N (for no), or U (for uncertain).

Was it worthwhile for you to participate in this research study? Y N U

If you had to do it over, would you participate in this research study again? Y N U

Would you recommend participating in this research study to others? Y N U

Overall, did your quality of life change by participating in this research study (circle one response)?

It improved It stayed the same It got worse

Overall how was your experience of participating in this research study (circle one response)?

Better than I expected The same as I expected Worse than I expected

If there was **one thing** that could have been done to improve your experience in this research study, what would it be?

_____

_____

Would you like to talk to someone about your concerns (circle one response)? Yes No

APPENDIX VI: EQ-5D-3L

EQ-5D-3L

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑

I have moderate problems walking ❑

I am confined to bed ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

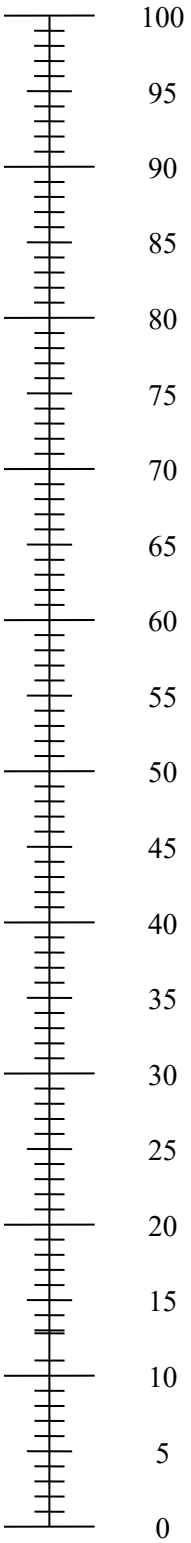
I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX VII HEALTH CARE EXPENSE DIARY AND QUESTIONNAIRE

Use this diary to record your health care-related expenses from the time you start radiation therapy until 2 to 8 weeks after you have completed radiation therapy. At your 2-8 week clinic visit, you will use this diary to complete the Health Care Expense Questionnaire.

Date	Type of expense			
	Travel	Lodging	Child Care	Work-related

Date	Type of expense			
	Travel	Lodging	Child Care	Work-related

Health Care Expense Questionnaire

Before you were diagnosed with breast cancer, did you do paid or unpaid work outside the home?
☐Yes ☐No

If you worked outside the home, which of the following best applies to you?
Paid work outside the home ☐Yes ☐No
Unpaid work outside the home ☐Yes ☐No (including work in a family farm or business).
Self-employed / business owner ☐Yes ☐No

If you worked outside the home:
How many days per week did you work? __ (days)
How many hours per day did you work? __ __ (hours)
What is your profession? _____
In what industry do you work? _____
What is / was your job title? _____

NOTE: This section is designed to capture the out of pocket expenses associated with radiation therapy.
How many hours were spent in total for each radiation treatment (time from leaving home/other accommodation or work to return to home/other accommodation or work)? __ __ (hours)
What is the distance from the radiation treatment facility from home/other accommodation or work? __ __ __ (miles)

Did you commute daily to radiation treatment from your home? ☐Yes ☐No
(If no), which of the follow apply (check one):

- ☐ I was in a health care facility during radiation
- ☐ I was living with a friend/family member during radiation (answer the commuting questions above and below as applicable)
- ☐ I stayed hotel, apartment, or similar facility during radiation (answer the commuting questions above and below as applicable)

If hotel, apartment or similar facility, estimated cost of lodging during your radiation treatment $__ __ __ __
(If yes), method of transport used to get to the radiation therapy facility (Check all that apply)

Car ☐Yes ☐No
(If yes) approximate cost for parking per visit $__ __.__ __
Did you drive yourself? ☐Yes ☐No
Were you driven? ☐Yes ☐No

Was it a combination of driving yourself or being driven ☐Yes ☐No

Shuttle ☐Yes ☐No

(If yes) Approximate cost per visit $__ __.__ __

Public transport ☐Yes ☐No

(If yes) Approximate cost per visit $__ __.__ __

On foot ☐Yes ☐No

Taxi/car service ☐Yes ☐No

(If yes) Approximate cost per visit (both ways) $__ __ __

Number of radiation treatments during which at least one other person accompanied patient __ __

Number of visits to radiation treatment facility since completing radiation therapy (follow up visits) __ __

From the 1st day of starting radiation, until 40 days after the completion of radiation:

Number of days the patient was unable to go to work at all __ __

Number of days the patient went to work part-time __ __

If part time, number of hours reduced from typical work day __ __

Estimate child care costs due to radiation therapy $__ , __ __ __

Estimate wages lost due to radiation therapy $__ __ , __ __ __

APPENDIX VIII PATIENT HEALTH CARE UTILIZATION DIARY

This diary is for your use to record your visits to health care facilities to help us complete a questionnaire 1 year after radiation. We would like to capture all visits to any medical facility related to your healthcare in the 1 year after completing radiation.

Types of visits to record:

Clinic visits to radiation oncology
Clinic visits to medical oncologist
Clinic visits to surgeon who performed mastectomy
Clinic visits to plastic surgeon
Visits to emergency room
Visits to physical therapist
Other health care services used that are not listed

Hospital admissions, also record days per each hospital admission
Surgical procedures to breast reconstruction, also record the name of each procedure

	Date	Type of visit	If hospital admission, number of days
1 Month after RT			
2 Months after RT			

	Date	Type of visit	If hospital visit, number of days
3 Months after RT			
4 Months after RT			
5 Months after RT			
6 Months after RT			
7 Months after RT			

	Date	Type of visit	If hospital visit, number of days
8 Months after RT			
9 Months after RT			
10 Months after RT			
11 Months after RT			
12 Months after RT			

APPENDIX IX BOOKLET ADMINISTRATION SCHEDULE (ENGLISH): FOR SITE CONVENIENCE ONLY

Booklet Name	Booklet Contains	Booklet Schedule
BOOKLET A (Pre-reconstruction)	Includes Breast-Q survey(mastectomy postoperative module), LBCQ, and EQ-5D-3L	Complete prior to RT (mastectomy or TE only)
BOOKLET A (Post-Reconstruction)	Includes Breast-Q survey(reconstruction postoperative module), BLE, LBCQ, and EQ-5D-3L	Complete prior to RT (definitive reconstruction)
BOOKLET B	**BLE**, LBCQ , and EQ-5D-3L	Complete 6 months post RT (**for BLE, when reconstruction completed, which may be up to 18 months out per protocol**)
BOOKLET C	EQ-5D-3L	Complete 12 and 18 months post RT
BOOKLET D	Breast-Q (reconstruction postoperative module), BLE, LBCQ, EQ-5D-3L, and Was it Worth It (WIWI) Questionnaire	Complete 2 years post RT
BOOKLET E	Breast-Q (reconstruction postoperative module), BLE, and LBCQ	Complete 5 years post RT
BOOKLET F	Patient Health Care Expense Diary and Health Care Expense Questionnaire	Give the patient health care diary and health care expense questionnaire (Appendix VII) prior to RT and to be returned at the 2-8 week
BOOKLET G	Health Care Utilization Diary	Give the patient health care utilization diary after radiation therapy (Appendix VIII) and this is to be returned at the 12 month visit