NRG ONCOLOGY
Radiation Therapy Oncology Group

RTOG 1005

(ClinicalTrials.gov NCT #:* 01349322*)

A PHASE III TRIAL OF ACCELERATED WHOLE BREAST IRRADIATION WITH HYPOFRACTIONATION PLUS CONCURRENT BOOST VERSUS STANDARD WHOLE BREAST IRRADIATION PLUS SEQUENTIAL BOOST FOR EARLY-STAGE BREAST CANCER

Amendment 5: December 16, 2021

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This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Cancer Research Group; and SWOG.

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☒ Approved International Member Sites

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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 www.ctsu.org, and select Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 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 https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	NRG Headquarters 50 S.16th Street, Suite 2800 Philadelphia, PA 19102 Do not submit study data or forms to CTSU Data Operations. 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 (https://www.ctsu.org). 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.		
For clinical questions (i.e. patient eligibility or treatment-related) Contact the Study Data Manager of the Lead Protocol Organization		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

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A Phase III Trial of Accelerated Whole Breast Irradiation with Hypofractionation plus Concurrent Boost versus Standard Whole Breast Irradiation Plus Sequential Boost for Early-Stage Breast Cancer

SCHEMA (6/21/11)

STRATIFY

Age
< 50 vs. ≥ 50

Chemotherapy
Yes vs. No

ER Status
+ vs. –

Histologic Grade
1, 2 vs. 3

RANDOMIZE

ARM 1: Standard fractionation
Whole Breast 50.0 Gy/25 fractions/2.0 Gy daily
Optional fractionation of 42.7Gy in 16 fractions permissible
Sequential Boost 12.Gy/6 fractions/2.0 Gy daily or
14.0Gy/7fractions/2Gy daily

ARM 2: Hypofractionation (15 fractions total)
Whole Breast 40 Gy/15 fractions/2.67 Gy daily
Concurrent boost 48.0 Gy/3.2 Gy daily

See Section 5.0 for pre-registration requirements
See Section 6.0 for details of radiation therapy

Patient Population: (5/6/2013) (See Section 3.0 for Eligibility and additional requirements)
pStage 0, I, II Breast Cancer resected by lumpectomy
ypStage 0, I,II Breast Cancer resected by lumpectomy that followed neoadjuvant systemic therapy

Required Sample Size: 2312

ELIGIBILITY CHECKLIST (5/6/2013)

NRG Oncology Institution #
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Case # **(page 1 of 4)**

_____(Y) 1. Does the patient have a pathologically proven diagnosis of breast cancer resected by lumpectomy?

_____(Y) 2 .Is the patient's stage of breast cancer one of the following? (A, B or C)

____**A.** pStage I, II breast cancer *AND* at least one of the following:

- Age < 50 years
- Positive axillary nodes
- Lymphovascular space invasion
- 2 or more close resection margins (> 0 mm to ≤ 2 mm)
- 1 close resection margin and extensive intraductal component(EIC)
- Focally positive resection margins
- Non-hormone sensitive breast cancer (ER and PR-negative)
- Grade III histology
- Oncotype recurrence score > 25

____**B.** pStage 0 breast cancer with nuclear grade 3 DCIS and patient age < 50 years

____**C.** ypStage 0, I, II breast cancer resected by lumpectomy after neoadjuvant systemic therapy

_____ (Y) 3. Is the patient female?

_____ (Y) 4. Will the patient be registered within 50 days from whichever is later: last surgery (breast or axilla) or last chemotherapy?

NOTE: The day of surgery is Day "0"

_____ (Y/N) 5. Does the patient have multifocal breast cancer?

_____ (Y) If yes, was it resected through a single lumpectomy incision with negative margins?

_____ (Y) 6. Has the patient had breast conserving surgery with margins defined as follows?

- Negative margins defined as no tumor at the resected specimen edge.
- Close resection margins; > 0 mm to ≤ 2 mm defined as:
  - One close resection margin and EIC
  - 2 or more close resection margins
- A focally positive resection margin

_____ (Y) 7. Was axillary staging performed as outlined in section 3.1.7 of the protocol?

_____ (Y) 8. Is the patient ≥ 18 years of age?

_____ (N) 9. Is there clinical evidence of distant metastases?

_____ (Y) 10. Was a history/physical examination, including breast exam and documentation of weight and Zubrod Performance status of 0-2 done within 28 days prior to study entry?

_____ (Y) 11. Was a right and left mammogram done within 90 days of diagnostic biopsy establishing diagnosis?

_____ (Y) 12. Does the patient have adequate bone marrow as specified in section 3.1.12 of the protocol

NRG Oncology Institution #
RTOG 1005 **ELIGIBILITY CHECKLIST** (1/9/14)
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_____ (Y/N) 13. Is the patient of childbearing potential?
____ (Y/N) if yes, is the patient sexually active?
____ (Y) 14a. If yes, is the patient willing/able to use medically acceptable forms of contraception during radiation therapy?

_____ (Y) 14. For women of childbearing potential, was a urine or serum pregnancy test negative within 14 days prior to study entry?

_____ (N) 15. Is the patient lactating?

_____ (N) 16. Is the patient's breast cancer stage AJCC pathologic T4, N2 or N3, M1 pathologic stages III or IV, breast cancer?

_____ (N) 17. Does the patient's treatment plan include regional node irradiation?

_____ (Y/N) 18. Has the patient had a prior invasive non-breast malignancy (except non-melanomatous skin cancer or carcinoma in situ of the cervix)?

_____ (Y) If yes, has the patient been disease free for a minimum of 5 years prior to study entry?

_____ (N) 19. Has the patient had a prior invasive or in-situ carcinoma of the breast (prior LCIS is eligible)?

_____ (N) 20. Does the patient have two or more breast cancers not resected through a single lumpectomy incision?

_____ (N) 21. Is the patient's breast cancer *only* DCIS (without an invasive component) and her age ≥ 50 years old?

_____ (N) 22. Does the patient have nuclear grade 1 or 2 DCIS *only* (without an invasive component) and is < 50 years old?

_____ (N) 23. Does the patient have invasive breast cancer and low risk for 5 year in breast recurrence after lumpectomy with negative margins and does not meet one of the eligibility factors in section 3.1.3 A.?

_____ (Y) 24. Is there a clear delineation of the extent of the target lumpectomy cavity for a boost on a CT scan for radiation treatment planning within 28 days prior to study entry?

_____ (N) 25. Are there suspicious unresected microcalcifications, densities, or palpable abnormalities (in the ipsilateral or contralateral breast) that were not biopsied and found to be benign?

_____(N) 26. Does the patient have non-epithelial breast malignancies such as sarcoma or lymphoma?

_____ (N) 27. Does the patient have Paget's disease of the nipple?

_____ (N) 28. Has the patient had prior radiotherapy to the breast or prior radiation to the region of the ipsilateral breast that would result in overlap of radiation therapy fields?

NRG Oncology Institution #
RTOG 1005 **ELIGIBILITY CHECKLIST** (5/24/11)
Case # **(page 3 of 4)**

_____ (N) 29. Does the patient's treatment plan include concurrent chemotherapy for the current breast cancer?

_____ (N) 30. Does the patient have active systemic lupus erythematosus, or any history of scleroderma, dermatomyositis with active rash?

_____ (N) 31. Does the patient have severe, active co-morbidity, as defined in section 3.2.17

_____ (Y) 32. Did the patient provide study specific informed consent prior to study entry?

_____ (N) 33. Does the patient have a medical or psychiatric condition that would prevent them from receiving the protocol therapy or providing informed consent?

The following questions will be asked at Study Registration:
"3D-CRT and IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION"

_____ 1. Institutional person randomizing case.

_____(Y) 2. Has the Eligibility Checklist been completed?

_____(Y) 3. In the opinion of the investigator, is the patient eligible?

_____ 4. Date informed consent signed

_____ 5. Patient's Initials (First Middle Last)

_____ 6. Verifying Physician

_____ 7. Patient ID

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Method of Payment

_____ 15. Any care at a VA or Military Hospital?

_____ 16. Calendar Base Date

_____ 17. Randomization date

NRG Oncology Institution #
RTOG 1005 **ELIGIBILITY CHECKLIST** (1/9/14)
Case # **(page 4 of 4)**

_____(Y/N) 18. Have you obtained the patient's consent for her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 19. Have you obtained the patient's consent for her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 20. Have you obtained the patient's consent for her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 21. Have you obtained the patient's consent for her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

_____(Y/N) 22. Have you obtained the patient's consent to allow someone from this institution to contact her in the future to take part in more research?

_____ (Y/N) 23. Patient has consented to participate in the Cosmesis Study? (***NOTE: Non-chemotherapy Cosmesis subset closed to accrual 3/8/13; chemotherapy Cosmesis subset closed to accrual 01/9/14***)

If no, provide reason:
1. Patient refused due to illness
2. Patient refused for other reason: specify _____
3. Not approved by institutional IRB
4. Tool not available in patient's language
5. Other: specify_____

_____ 24. Age (< 50 vs. ≥ 50)

_____(Y/N) 25. Intention to receive chemotherapy (before receiving protocol RT) (yes vs. no)

_____(Y/N) 26. ER Status (positive vs. negative)

_____ (Y/N) 27. Specify Radiation Technique (3D-CRT vs. IMRT) (see section 6.4.3. for definition)

_____ 28. Histologic Grade (G1-2 or G3)

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/NRG Oncology audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Breast-Conserving Surgery and Radiation for Early Staged Breast Cancer

Breast-conserving surgery and RT are standard alternatives to mastectomy for eligible patients with stage I and II invasive breast cancer (NIH Consensus Conference 1991; National Comprehensive Cancer Network 2010). Post lumpectomy RT is associated with long-term local control on the order of 85-95% with equivalent survival outcomes as mastectomy (Veronesi 2002; Fisher 2002). The reduction in local recurrence from radiation post lumpectomy has also been associated with improved overall survival compared to surgery alone (Early Breast Cancer Trialists' Collaborative Group 2005). Therefore it is imperative that new radiation methods post lumpectomy are not inferior in terms of local control so that there is not a potential impact on disease free or overall survival.

In spite of these benefits of RT, the number of women treated with breast-conserving surgery but without RT is approximately 15-20% (Morrow 2001; Polednak 2002). One problem with conventional RT to the whole breast may be the 6-7 week length of treatment. A conventional schedule given up to 6-7 weeks involves treatment of the whole breast at 1.8 - 2 Gy daily fractions for 46 - 50.4 Gy, followed by a sequential boost to the tumor bed for 10-18 Gy. Methods for reducing overall treatment time may improve the utilization of postoperative RT in eligible women after breast-conserving surgery.

Some methods for shortening overall treatment time (e.g., partial breast RT and intraoperative RT) limit radiation to the region of the primary tumor alone with a small margin and omit RT to other quadrants of the breast. Not all patients are eligible for these methods that require patients with small tumor sizes (≤ 3 cm) and favorable histologic characteristics (no extensive intraductal component, no lymphovascular space invasion, negative or 1-3 axillary lymph nodes). In addition, the long-term efficacy of partial breast irradiation compared to WBI is being studied in ongoing clinical trials including NSABP B-39/ RTOG 0413.

1.2 Whole Breast, Hypofractionated Radiation in Early Stage Breast Cancer.

Hypofractionation, or delivery of greater than standard 1.8 - 2 Gy fraction sizes per day, is a method of shortening overall treatment time in breast cancer. There are many potential benefits in delivering postoperative WBI in a shorter period of time. The advantages include greater convenience for patients, broad applicability to nearly all patients following lumpectomy, improved use of postoperative radiation for breast conservation, decreased treatment costs, and increased utilization of existing RT resources.

Historically, standard fraction sizes of 1.8-2.0 Gy for radiotherapy were based primarily on studies examining squamous cell cancers from cervix and head and neck regions. The smaller fraction sizes exploited a biological differential in squamous cell cancer fractionation sensitivity versus normal tissue fractionation sensitivity. This allowed relative sparing of surrounding normal tissue from low dose per fraction. However, investigators from the United Kingdom hypothesized that the fractionation sensitivity for adenocarcinoma of the breast is close to that of the normal breast tissue and therefore with increasing fraction size a sufficiently large reduction of total dose could be implemented to keep late toxicity constant without losing tumor control.

Four prospective randomized clinical trials have shown promising results with hypofractionated schedules for WBI (Yarnold 2005; Owen 2006; START A, START B 2008; Whelan 2010). In each of these studies, the goal was to deliver a hypofractionated dose schedule that is biologically equivalent to the standard fractionation breast dose of 50 Gy in 25 fractions of 2 Gy. With 5-10 year follow-up of these studies, there has been

similar in-breast local control between the hypofractionated and standard fractionated arms.

Despite these data, widespread adoption of hypofractionated whole breast irradiation has been hampered because of two remaining questions:
1). What is the optimal method to deliver the boost to the tumor bed and the outcome with hypofractionation, for those higher risk breast cancer cases requiring boost? ; and
2). Will newer CT based radiation delivery methods that have emerged using standard fractionated WBI demonstrating reduced acute and late toxicity have equivalent results in hypofractionated schedules?

This proposed study is designed to address these questions by:
1). Evaluating a hypofractionated dose schedule that is biologically equivalent for both the whole breast dose AND the higher boost dose to the breast tissue at greatest risk of recurrence immediately around the lumpectomy cavity; and
2). Comparing early and late toxicity after standard and hypofractionated radiotherapy when adopting CT based WBI treatment delivery methods with 3-dimensional conformal radiation therapy (3DCRT) or intensity modulated radiation therapy (IMRT).

1.3 Tumor Bed Boost

Of the 4 prospective studies for hypofractionated WBI, one did not use a boost, 2 used a boost at the discretion of the treating department policy, and only 1 examined the boost in a prospective fashion. In all cases the boost was delivered with standard fractionation. The boost dose was 10 Gy in 5 fractions in the START trials and 14 Gy in 7 fractions in the earlier RMH/GOC trial. The boost was given sequentially in all 3 trials. The use of a sequential boost of 1-2 weeks in these studies extended the overall treatment time to nearly 5 weeks in some cases reducing the potential time-saving benefit to patients. None have data on a hypofractionated boost dose schedule that is biologically equivalent to the cumulative dose from a conventional tumor bed boost.

Table 1: Boost in randomized trials of whole breast hypofractionation

Study	#	Fractionation Schedule	% Boost	Cosmetic Outcome % Good/excellent	Time Point
Canadian	612	50 Gy / 25	0	71.3	10 years
	622	42.5 Gy / 16	0	69.8	
RMH/GOC	470	50 Gy / 25	74.5**	71	10 years
	466	42.9 Gy / 13		74	
	474	39 Gy / 13		58	
START A	749	50 Gy / 25	60.4	60*	5 years
	750	41.6 Gy / 13	61	58*	
	737	39 Gy / 13	60.5	66*	
START B	1105	50 Gy / 25	41.4	61*	5 years
	1110	40 Gy / 15	43.8	66*	

* No moderate/marked change in breast appearance
** Distribution by trial arm not stated

In the RMH/GOC trial, 723 patients were randomized to boost versus no boost. A further 687 patients were recommended an elective boost but not randomized. The 10–year % good or excellent cosmetic result was 66% randomized to no boost, 70% randomized to a boost, and 70% non-randomized receiving boost (p=not significant).

In two prospective randomized studies in invasive breast cancer, the use of a boost after WBI reduced the risk of local recurrence even in patients with negative resection margins (Romestaing 1997; Bartelink 2007). In the first trial, patients were randomized to 10 Gy boost after 50 Gy whole breast irradiation. At 5 years, the risk of local recurrence was

3.6% versus 4.5% (P = .044). In the EORTC trial, patients were randomized to a 16-Gy boost after 50 Gy to the whole breast. The overall local recurrence rates were 10.2% without a boost and 6.2% with a boost, respectively, a proportional reduction of 40%, which was statistically significant This reduction occurred for patients of all ages but was greatest in absolute terms for women age 40 years or younger (from 23.9% to 13.5%) and ages 51 – 50 years (12.5% to 8.7%). An international survey of Radiation Oncologists in 2001-2002 showed that 85% of American and 75% of European respondents would deliver a boost even with negative margins after WBI (Ceilley 2005). Current guidelines by the National Comprehensive Cancer Center Network (NCCN) suggest that a boost may not be required in all patients (National Comprehensive Cancer Network 2009). This reflects the understanding that the magnitude of the benefit of the boost may be smaller in some subgroups of patients as seen in the EORTC boost trial. The consensus guidelines for 2009 indicate that a boost is recommended for patients aged < 50 years, positive axillary nodes, positive lymphovascular space invasion, and/or close/positive resection margins. A boost in other low risk groups is considered optional.

In both prospective randomized studies in invasive breast cancer testing the use of a sequential boost, the addition of the boost increased the incidence of late effects such as telangiectasias and fibrosis (Romestaing 1997; Bartelink 2007). Therefore, how a boost will impact efficacy, cosmesis and risk of complications is essential if hypofractionation is to become more widely adopted.

This proposed study will evaluate a hypofractionated dose schedule biologically equivalent to the cumulative tumor bed dose given with sequential boost after WBI but to be delivered concomitantly during 15 fractions of hypofractionated WBI.

1.4 Conformal Radiation Methods in Early Stage Breast Cancer.

Initial experiences with IMRT for breast cancer have shown clinical feasibility, improved dose distributions in the treated breast, lower doses given to normal heart or lung tissue compared with standard techniques, and a low incidence of acute toxicity (Vicini 2002; Chui 2002; Freedman 2006).

Vicini, et al. (2002) reported on 281 patients with stage 0, I and II breast cancer treated with an IMRT technique. The rate of acute grade 2 skin toxicity was 43%, and the rate of acute grade 3 skin toxicity was 1%. Cosmesis at 1 year was good or excellent in 99% of patients. Harsolia, et al. (2007) reported on a series of 172 patients, 93 treated with IMRT and 79 with conventional radiation. They showed that IMRT results in a significant decrease in acute dermatitis, edema, and hyperpigmentation and a reduction in the development of chronic breast edema compared with conventional wedge-based radiation. In one randomized trial from the United Kingdom reported by Donovan et al of standard radiotherapy versus IMRT/3DCRT in early-stage breast cancer, 240 of 306 patients were able to be evaluated by photographs for change in breast appearance (Donovan 2007). There was a negative change in breast appearance in 58% of patients randomized to 2D conventional treatment compared to 40% randomized to IMRT. In a second randomized trial from Canada of 358 patients, Pignol, et al.(2008) compared standard wedge compensated conventional radiation to IMRT/3DCRT and found that IMRT was associated with improved dose homogeneity and reduced moist desquamation (31% vs. 48%, p=0.0019).

These randomized trials demonstrated reduced toxicity from standard fractionation WBI delivered with IMRT/3DCRT compared to 2D delivery methods. An important question is whether similar results as IMRT can be achieved with 3DCRT methods that give comparable coverage of the entire breast volume and exclusion of normal tissues on CT. To fully evaluate this, it is first necessary to establish target doses, normal tissue constraints, acceptable heterogeneity, and appropriate quality assurance for the delivery of WBI with CT-based volumes with 3DCRT and IMRT. These parameters are not precisely known today.

1.5 Hypofractionation and Concurrent Boost

There are 3 recent Phase I/II trials showing the safety and short-term efficacy of hypofractionated radiation therapy with a concurrent boost:

1) Freedman, et al. (2007) have reported a clinical study of hypofractionation using IMRT and an incorporated breast boost in early-stage breast cancer. Seventy-five patients were treated on study. The whole breast was treated to a dose of 2.25 Gy per day for 20 fractions for a total of 45 Gy. The incorporated boost gave simultaneously the tumor bed 2.8 Gy per fraction for 20 days for a total of 56 Gy. This use of hypofractionation of the whole breast volume, and simultaneously the boost volume, results in a 4-week overall treatment time. The maximum acute skin toxicity by the end of treatment was grade 0 in 9 patients (12%), grade 1 in 49 (65%), and grade 2 in 17 (23%). There was no grade 3 or higher skin toxicity. The maximum skin toxicity varied by breast size: Small 100% grade 1 (n=12); medium 6% grade 0, 80% grade 1 and 14% grade 2 (n=35); and large 4% grade 0, 48% grade 1 and 48% grade 2 (n=23). After radiation, all grade 2 toxicity had resolved by 6 weeks. Hematologic toxicity was grade 0 in most patients except for grade 1 neutropenia in 2 patients and grade 1 anemia in 11 patients. With a median potential follow-up of 54 months, the 5-year local recurrence rate was 1.4%. There were no significant differences in baseline versus 32 month post-treatment patient-reported or physician-reported cosmetic scores.

2) Formenti, et al. (2007) have also reported a trial of IMRT, hypofractionation, and concomitant boost. A dose of 40.5 Gy was delivered in 15 fractions with a concomitant boost of 0.5 Gy per day for a total tumor bed dose of 48 Gy. The results in 91 patients treated were reported with a median follow-up of 12 months. The major acute toxicity was reversible grade 1-2 dermatitis in 67%. There were no treatment breaks. There were 2 acute grade 3 toxicities, 1 skin and 1 fatigue. There were no late grade 3 toxicities. Late fibrosis was reported grade 1 in 48%, grade 2 3%. Grade 1 pigmentation change was noted in 70%. Breast pain was grade 1 in 8% and grade 2 in 2%. Skin telangiectasias were grade 1 in 3% and grade 2 in 2%. There was 1 regional node recurrence.

3) Chadha, et al.(2009) have reported a trial of conventional whole breast irradiation with a concomitant boost over 3 weeks for early stage breast cancer. The whole breast dose was 2.7 Gy per fraction for 15 fractions to a dose of 40.5 Gy. The concomitant boost to the lumpectomy site was a total of 3 Gy per fraction for 15 fractions to a total dose of 45 Gy. The results of 105 patients were reported at a median follow-up of 24 months. There was no acute grade 3 or 4 toxicity. There were no reported late soft tissue toxicities. There was no significant negative effect reported on cosmesis.

1.6 Radiobiologic Rationale for Proposed Trial of Hypofractionation and Concurrent Boost

The radiobiology co-investigators for this trial were participants of the UK START trials and Formenti trials. They developed the dose regimens used in the proposed trial. Based on the best available estimates of the fractionation sensitivity, quantified by the α/βratio of the linear-quadratic (LQ) model, for subclinical breast cancer and changes in breast appearance derived from the UK fractionation trials, it is possible to estimate the biologically equivalent doses in 2-Gy fractions delivered to the whole breast and the tumor bed. The two START trials, the Royal Marsden-Cheltenham pilot trial and the OCOG trial randomized more than 7,000 women to moderately hypofractionated schedules, confirming the validity of the LQ model effect estimates at least up to 3.3 Gy per fraction.

1.6.1 Whole Breast Volume

The WBI fractionation schedule in the control arm is 50 Gy in 25 fractions over five weeks for the whole breast irradiation. This is also the control arm in the ongoing NSABP B-39 / RTOG 0413 phase III trial. 42.5 Gy in 16 fractions as used in the

Canadian hypofractionated trial is also permitted. The WBI dose-fractionation in the experimental arm is identical to the schedule used in the UK START B trial in the hypofractionation arm, 40 Gy in 15 fractions, 2.67 Gy per fraction over 3 weeks.

There is evidence that the tumor control effect of the WBI in the experimental arm will be noninferior to the WBI dose fractionation used in the control arm. In the START B trial (2008), the WBI dose fractionationation produced a 5-year estimate of local-regional relapse of 2.0% with hypofractionation compared with 3.3% in the standard 2 Gy control arm of that trial . This is consistent also with the 10-year estimates of local relapse of 6.2% for 42.5 Gy in 3 weeks and 6.7% for 50 Gy in 5 weeks in the Canadian hypofractionation trial (Whelan 2010).

1.6.2 Boost

The sequential tumor bed boost in the control arm is minimally 12Gy in 6 fractions, or minimal total of 62 Gy to the tumor bed or maximally 14 Gy in 7 fractions, or a maximal total of 64 Gy to the tumor bed. The concurrent boost dose-fractionation in the experimental arm is 48.0 Gy in 15 fractions of 3.2 Gy.

A concurrent boost to the tumor bed delivering a total dose of 48.0 Gy in 15 fractions with 3.2 Gy per day would result in an equivalent tumor bed dose (assuming an alpha beta ratio of 4, and correcting for proliferation effects) in 2-Gy per fraction of approximately 63-66 Gy in 2 Gy fractions (with the range due to an estimate for increased biologic effectiveness due to the fewer weeks of treatment with a concurrent rather than sequential boost). This dose for the concurrent boost was developed with the input of our radiobiology co-investigators Soren M. Bentzen, PhD, DSc and Barry Rosenstein, PhD who have both been involved in prior trials of breast hypofractionation.

1.7 Other Questions That Remain About Whole-Breast Hypofractionated Radiation

Despite the prior randomized trials, many questions still remain regarding the use of WBI hypofractionated schedules.

1.7.1 Length Of Treatment

The length of treatment varied in these prospective trials of hypofractionation. The Ontario Clinical Oncology Group (OCOG) study finished in 3 weeks but no boost was used. The trials by the United Kingdom used every other day fractionation in order to keep the overall treatment time for the WBI component constant at 5 weeks, which is not used in the United States. The exception is the START B trial where WBI was finished in 3 weeks in the hypofractionation arm, but then followed by a boost of 10 Gy in 5 fractions over an extra week in some 40% of the cases according to departmental policy or physician preference. A prospective cooperative group trial of 3 week fractionation that includes a boost has not been completed.

1.7.2 Breast Size

Few studies treated large breast sizes to any significant degree. Only the OCOG study provided an objective measurement of breast size using the patient chest wall separation, and then used this cut-off as an exclusion criterion. There was no doubt a concern that with conventional radiation used in these trials, the baseline risk of acute dermatitis or late fibrosis would be greater in large breasted women. Radiation dermatitis is most directly related to increased dose inhomogeneity, which itself is most directly related to increasing breast size or chest wall diameter (Pignol 2008; Das 1997). And moist desquamation is more common in women with large breasts than those with small breasts (Freedman 2006; Fisher 2000). So enrolling physicians may have felt that if this baseline was higher with conventional radiation, then how much more so could it have been with hypofractionated radiation? However, since the outcomes of these studies have now shown comparable acute and late long-term outcomes, further study is needed to determine whether this is only applicable to women mostly with small or medium-sized breasts included in these studies.

1.7.3 Radiation Sequencing With Chemotherapy

The trials of whole-breast hypofractionation consisted of mostly lower-risk patients so that the number treated with systemic chemotherapy was low (11-36%). As a result, the applicability and safety of fractionation schedules used in these trials to the majority of patients that are now treated with adjuvant systemic chemotherapy is not well known. Potential for added complications of radiation in chemotherapy-treated patients include fatigue, cytopenias, and infection. Use of chemotherapy has also been associated with a worse long-term fibrosis and cosmetic outcome in some studies,(Abner 1991) mostly with concurrent rather than sequential sequencing (Abner 1991;Toledano 2006). However, these older studies used predominately cyclphosphamide-methotrexate-5-fluorouracil-based regimens (CMF), and the results may not be applicable to patients treated with the anthracycline- and taxane-based regimens now in use today. The potential for added acute or late toxicity with hypofractionated radiation in women treated with modern chemotherapy regimens needs further study.

1.7.4 High-Risk Patients

There are several clinical and pathologic factors that have been associated with an increased risk for local recurrence after breast-conserving surgery and radiation. These include young patient age (Fisher 2001;Taghian 2004; Freedman 2002;) a positive or close (< 2mm) margin (Veronesi 1995b; Freedman 1999; Park 2000), the presence of an extensive intraductal component (EIC) -positive tumor (Veronesi 1995b; Freedman 1999; Park 2000; Veronesi 1995) estrogen receptor-negative tumors (Wapnir 2006), and lymphovascular invasion (Veronesi 1995; Borger 1994). It is in these patients that the potential benefit of a radiation boost is greatest. For example, younger age was associated with a greater observed absolute risk reduction at 10 years in one randomized trial 14. The risk of local recurrence was reduced from 23.9% to 13.5% in those aged ≤ 40 years, from 12.5% to 8.7% in the 41- to 50-year age group, from 7.8% to 4.9% in the 51- to 60-year age group, and from 7.3% to 3.8% in those older than 60 years. There was relatively low enrollment of patients with young age, positive nodes or close margins on the available randomized trials of whole-breast hypofractionation. Since most of these trials either treated lower-risk patients exclusively or did not stratify randomization based upon risk, it is also uncertain how the results of these trials can been applied to the majority of patients seen and treated with BCT. This trial is to have an eligibility criterion that will selectively enroll patients at an increased risk for local recurrence. The estimate of 5-year local recurrence in the control arm of 2 Gy per fraction is 6%. Table 2 shows data from recent prospective trials containing results in subgroups of high-risk patients similar to the expected enrollment of this trial.

Table 2: 5-Year Local Recurrence after BCS + RT in prospective randomized trials

Trial	Years	Subgroup	5-Year IBTR (%) 2 Gy fractionation	5-Year IBTR (%) Alternate fractionation	
Whelan (OCOG)	1993 - 1996	All WBI	3.2	2.8	
		Age < 50	7.2	3.6	
		T-2 size	5.4	6.4	
Yarnold (START A)	1998 - 2002	All WBI + 60% boost	3.6	3.5†	5.2†
		Age < 50	7.4	2.9	7.1
		Grade 3	7.3	4.6	6.9
		Node positive	6.6	6.7	4
		Age < 50 OR grade 3 OR node positive	5.5	4.4	6.1
Yarnold (START B)	1999 - 2001	All WBI + 60% boost	3.3	2.2	
		Age < 50	4.8	4.1	

		Grade 3 Node positive Age < 50 OR grade 3 OR node positive	7.6 7.7 5.6	3.9 4.4 3
Owen/Yarnold (RMH/GOC)	1986 - 1998	All WBI + 74% boost	7.9	7.1† | 9.1†
Bartelink (EORTC)	1989 - 1996	Age ≤ 40 Age 41-50 Grade 3	10 6 7	-
Anderson (NSABP)	1981 - 2007	All node negative Node negative and age ≤ 49 Node negative and ER negative	3 5 5	-
Holli (Helsinki)	1990 - 1999	Age ≤ 50	17	-
Bear (NSABP B-27)	1995 - 2000	With AC chemotherapy With AC and T chemotherapy	7 3-4	-
Wapnir (NSABP)	1984 - 1994	All node positive Node positive and age ≤ 49 Node positive and ER negative	6 8 8	-
Sartor (CALGB)	1994 - 1997	With AC chemotherapy With AC and T chemotherapy	10 4	-
Veronesi (Milan)	1985 - 1987	Age ≤ 45 Age 46 – 55 Extensive in-situ component Margins positive	8 13 30 15	-
Fisher (NSABP)	1988 – 1993	All patients Age ≤ 49	7.9 12.9	-
EBCTCG	1976 – 1998	Node negative and age < 50 Node negative and grade 3 Node negative and T2 Node negative and ER poor	11 12 14 12	-

† = results for the 2 hypofractionated trial arms shown
References: (Veronesi 1990; Veronesi 1995; Fisher 1998; Mariani 1998; Bartelink 2001; Whelan 2002; Early Breast Cancer Trialists' Collaborative Group 2005; Sartor. 2005; Yarnold 2005; Bear et al. 2006; Owen 2006; Wapnir 2006; Bartelink 2007; The START Trialists' Group 2008; The START Trialists' Group 2008; Anderson 2009; Holli 2009; Jones 2009; Whelan 2010; Yarnold 2010)

1.7.5 Cardiac Toxicity

The randomized trials of breast hypofractionated radiation do not have sufficient follow-up to detect differences in late cardiac mortality. A large meta-analysis revealed a small but negative impact of RT on non-breast mortality but this effect took 10 or more years to become evident 5. The risk of radiation-related cardiac mortality has generally decreased over time (Giordano 2005), so that modern studies limited to patients treated with postlumpectomy radiation have not generally found differences in cardiac mortality between left- and right-sided irradiation (Borger 2007;Harris 2006). In a study of hypofractionation comparing ≤ 2 Gy to > 2 Gy fraction sizes, no difference in cardiac mortality was seen with a median follow-up of 7.9 years (Marhin 2007). This needs to be confirmed with longer follow-up of hypofractionation particularly in higher risk patients also receiving cardiotoxic chemotherapy regimens, such as dose-dense doxorubicin, taxanes and traztuzumab.

Nonfatal cardiac events have not been sufficiently reported in the randomized trials with hypofractionation either. Previous studies of conventional radiation fractionation have shown an increase in the number of nonfatal cardiac events associated with left breast

irradiation. In a study of patients treated in the Netherlands between 1980 to 1993, there was a non-significant increase of the relative risk of cardiovascular disease of 1.57 (95% confidence interval, 0.83-3.0) after left-sided radiation (Borger 2007). A study from the University of Pennsylvania showed that 10% of patients treated to the right breast had developed coronary artery disease by 20 years after treatment, compared to 25% of patients with left-sided cancers (Harris 2006). A group at the University of Michigan studied patients treated from 1984 to 2000 and observed a cumulative incidence of myocardial infarction/coronary artery disease requiring intervention of 2.7% at 10 years (Jagsi 2007).

Because of the relatively small numbers of cardiac events expected in this trial, limitation of cardiac risk to women with left-sided treatment, and difficulty in trial feasibility to obtain the long-term follow-up necessary to observe cardiac toxicity after 5-10 years, surrogate measures are needed to assess cardiac risk. NTCP calculations have been previously used to model cardiac risk in patients treated with external beam irradiation for breast cancer (Gagliardi 1996; Hurkmans 2002; Muren 2002; Hiatt 2006). In this study, we propose to use NTCP calculations from planning CT scans to collect data on the potential risk of cardiac complications for hypofractionated versus conventionally fractionated radiation.

1.8 Standardization of IMRT and 3DCRT for WBI

One of the most important issues concerning IMRT and 3DCRT for breast cancer is the accurate definition of target volumes. Conventional radiation techniques for breast cancer have been based solely on clinical palpation of breast tissue and bony chest wall anatomy. In contrast to standard techniques, IMRT and 3DCRT requires a volume-based target to create conformal dose distributions. Since there may be a significant variation among physicians regarding the definitions of breast tissue target and regional nodal volumes, efforts to define accurately the location of boundaries of the breast tissue and lymph nodes are needed. A consensus committee within the RTOG has developed guidelines for the definition of clinical target volumes and normal structures on CT for radiation treatment planning. This atlas will be adopted for the definitions used in radiation treatment planning for this study (Li 2009; White 2010).

IMRT will also require the development of acceptance criteria for judging the adequacy of any given treatment plan. Conventional 2D radiation was judged by a single transaxial isodose distribution through patient isocenter that under-represented the total breast volume or coverage of anatomy on a 2D port film. IMRT requires standardized benchmarks for assessment of dose-volume histograms for coverage of the targeted CT breast volumes and exclusion of normal structure volumes, e.g. lung and heart. Lastly, there is considerable variation in what constitutes IMRT in the technical aspects of delivery. Although the limited single institutions' results of using IMRT for breast cancer are promising, acceptable IMRT techniques need to be standardized and validated in a multi-institutional setting.

1.9 Tissue Banking for Future Translational Research

Blood samples will be banked for correlative studies to identify gene expressions predictive of radiation toxicity. Tumor samples will be banked to correlate genes that may be predictive for cancer recurrence, and for use in comparison studies with adjacent normal breast tissue to correlate with late toxicity.

1.9.1 Single Nucleotide Polymorphisms (Snps)

Late toxicity from WBI including fibrosis, skin atrophy and telangiectasia can occur in up to 20% of cases from standard fractionation (Meric 2002). Certain treatment factors, such as large fraction size, use of bolus and total dose, as well as, patient factors including breast size and patient body mass, are well recognized to be associated with higher late toxicity rates. It is a compelling hypothesis that certain genotypes are associated with more toxicity from radiation (Ho 2006). Gene polymorphisms of

transforming growth factor ß1 (TGF ß1) have been correlated with more severe fibrosis in breast cancer patients (Quarmbly 2003; Giotopoulos 2007) although independent validation studies are much needed. We hypothesize that certain gene expressions will correlate with individuals who are prone to late toxicity from WBI and/or will have a worse/better outcome from hypofractionated regimens.

Although there may be dosimetric explanations or underlying medical conditions responsible for the development of acute and chronic normal tissue toxicities following radiotherapy for breast cancer, this explanation is not the case for many patients. Often, the adverse response is simply ascribed to unknown individual variations, but evidence in support of genetic factors being responsible for individual variation in radiosensitivity between patients has been obtained (Safwat 2002). The development of an in vitro radiosensitivity assay capable of predicting the extent of normal tissue damage in radiotherapy patients therefore represents a long sought after goal (Fletcher 1988). Despite limited success, the effort to achieve this objective continues since an assay capable of predicting susceptibility for the development of adverse radiation effects would allow customization of radiotherapy protocols on an individual basis. By doing so, it has been estimated that a significant improvement in the therapeutic index could be achieved (Tucker 1996; Mackay 1999). The goal of this field of research, which has been termed “radiogenomics”, is therefore to develop a robust, specific assay for cancer patients eligible for radiotherapy to enable individual dose adjustment based upon the response of each patient to this test (Tucker 1996; Mackay 1999; Mackay 1998; Agren 1990). Of equal importance, knowledge of the genes whose alteration is associated with the development of radiation-induced normal tissue toxicities may provide important evidence as to the molecular pathways involved in the development of these radiation effects.

Substantial work has been performed in recent years in an effort to identify the genetic markers associated with an altered response to a standard radiotherapy protocol. Single nucleotide polymorphisms (SNPs) represent common genetic alterations found in human populations in which an alternate base pair is substituted for the normally observed base pair. A widely accepted threshold for a SNP is that the minor allele must be present in at least 1% of the population. However, many SNPs are present at a lower frequency and are sometimes referred to as rare variants. SNPs occur approximately once every 1,000 nucleotides in the human genome. Thus, it is roughly estimated that there are approximately 10 million SNPs present in human populations. The term “association”, as used in this context, indicates that possession of the minor allele for the SNP is associated with either an increase or decrease in the incidence of the normal tissue toxicity compared with subjects that harbored the major allele for the particular SNP.

The results of approximately 50 candidate gene studies to identify SNPs associated with a variety of radiation-induced normal tissue toxicities have been published (Andreassen 2009; Barnett 2009; Popanda 2009). Through this work, statistically significant associations with SNPs in the following genes with normal tissue toxicities following breast radiotherapy have been identified; ABCA1, APE1, ATM, CD44, eNOS, GSTA1, GSTP1, IL12RB2, LIG3, MAD2L2, MPO, PTTG1, RAD9A, SOD2, TGFB1, TP53, XRCC1 and XRCC3.

It should be noted that among this list of genes, ATM and TGFB1 have been the focus of multiple studies, whereas the other genes have been screened in only one or two studies. We are therefore proposing a novel “alpha-spending function” approach to the statistical analysis of these data for association. Thus, we will test TGFB1 and ATM SNPs at a significance level of 0.02. This would provide close to the same power as a study targeting just those SNPs in isolation. For the next 16 genes, we will test at the

0.0007 level. Using this data analytic strategy, the total type I (false-positive) error probability becomes 5%.

We assume, conservatively, that 1,200 patients will be genotyped. Assume further that the prevalence of the genotype of interest is 17% and that the incidence of late toxicity is 20% in the non-carriers. Testing at a nominal level of 0.0007 provides 90% power to detect an odds ratio of 3.5. Testing at a nominal level of 0.02 provides 90% power to detect an odds ratio of 1.9.

Although a series of candidate gene SNP studies has already been performed and several genome wide association studies are underway, a significant limit on the progress in radiogenomics is the lack of validation studies for SNPs that are identified in preliminary studies. Thus, the subjects to be screened in this study serve an important purpose as a validation population, the results of which will either act to confirm or refute the findings of initial studies.

The subjects in this study will be genotyped using the SNPlex assay which uses the Applied Biosystems oligonucleotide ligation assay (OLA) to achieve allelic discrimination and target amplification. The chemistry is made possible through the use of a set of universal core reagent kits and a set of SNP-specific ligation probes. Each assay includes three SNP-specific ligation probes: Two of the probes are allele-specific oligos (ASOs). These are designed specifically for the detection of SNPs by having the discriminating nucleotide on the 3′ end. Each ASO probe sequence also contains one of 96 unique ZipCode™ sequences for ZipChute™ probe binding. The third probe is a locus-specific oligo (LSO). Its sequence is common to both alleles of a given locus and anneals adjacent to the SNP site on its target DNA. Genotyping will be accomplished for the 18 genes listed above for which an association with the development of normal tissue toxicity in breast cancer radiotherapy patients has been identified. Since the SNPlex assay is more efficiently performed for blocks of 48 SNPs, this total number of SNPs will be genotyped in these 18 genes. Thus, 2-3 SNPs will be genotyped for each gene, focusing upon the SNPs that initial reports have associated with radiation-induced effects.

1.9.2 Breast Cancer Subtyping

Gene expression profiling by microarray has been increasingly used to develop predictive assays and prognostic systems for breast cancer treatment and outcome. An example of this is the 21 gene assay (Oncotype Rx) that can predict risk of distant metastases and relative chemotherapy benefit in estrogen receptor positive, node negative breast cancer patients that undergo anti endocrine therapy (Paik 2004) and has recently been shown to predict local failure (Mamounas 2010). In addition, the use of gene expression profiling and hierarchical clustering analyses has led to the classification of breast cancer into 5 groups based on patterns in gene expression: Luminal A, Luminal B, Basal Like, HER-2 enriched, and Normal like (Sorlie 2001). These subtypes have been correlated with distinct clinical phenotypes and to prognosis for overall and relapse free survival in various datasets (Sotiriou 2003; Carey 2006). The breast cancer subtypes have also been correlated with neoadjuvant chemotherapy response, with a higher likelihood of pathologic response associated with the basal-like and HER-2 enriched subtypes. Much less is known for the association of these subtypes with local-regional relapse and the interaction with radiation.

Estrogen (ER)/progesterone (PR) receptor, HER2, and cytokeratin (CK) immunohistochemistry (IHC) have been used as a surrogate for the molecular subtypes because of the technical limitations to date of performing microarray expression analysis on formalin fixed, paraffin embedded tissue. The marker combinations that are used to match the breast cancer subtypes are: luminal A: ER+ and/or PR+, HER2 -; luminal B: ER+ and/or PR+, HER2 +; basal-like: ER-, PR-, HER2 -, cytokeratin5/6+

and/or EGFR+; and HER2 enriched: ER-, PR-, HER2 +. Using markers as a surrogate, there have been a few studies that have retrospectively examined subtype to identify a relationship with local regional relapse demonstrating mixed results:

1) Kyndi, et al. (2008, 2009) reported that breast cancer subtyping was correlated with local-regional recurrence. However, this study was in the postmastectomy setting, had more advanced stages of disease, and in retrospect suboptimal systemic therapy – all factors that limit applicability to the patient population to be included in this study.

2) Millar, et al. (2009) used 5 biomarkers, ER, PR, HER2, CK 5/6 and EGFR IHC as surrogates for the intrinsic molecular subtypes to retrospectively examine 498 breast cancer patients who had undergone breast conservation therapy to identify any relationship with clinical outcomes. No correlation of subtypes with in-breast cancer recurrence was found, but a significant difference was observed for overall survival.

3) Freedman, et al. (2009) also did not find a correlation with local control and basal-like breast cancer in patients treated with breast conservation including standard fractionated radiation.

4) Nguyen, et al. (2008), retrospectively evaluated subtype, using ER, PR, and HER2 biomarkers as surrogates, in 793 breast cancer patients who had undergone breast-conserving therapy and found that the basal-like and HER2-enriched subtypes were significantly associated with increased rates of in-breast recurrence.

These and other studies have evaluated the impact of intrinsic breast cancer subtype only in patients treated with standard radiation fractionation of 2 Gy per day. A subset analysis of the 10 year outcomes from the Ontario Clinical Oncology Group randomized trial comparing standard fractionation to hypofractionation revealed that breast cancer patients with Grade III histology had significantly worse in-breast cancer recurrence rates in the hypo fractionated arm (4.7 % vs. 15.6%) (Whelan 2010). This suggests that the alpha/beta ratio and the effect of hypo fractionation may vary across different breast cancer cohorts, including intrinsic subtypes.

The development of RT-PCR based approaches that will permit subtyping from paraffin embedded specimen blocks, such as the recently reported PAM50 assay that identified a 50 gene subset to reliably classify into the previously described 5 breast cancer subtypes (Parker 2009), will more readily allow for future analysis for intrinsic subtype in studies like this one. Future correlative studies for this concept include an analysis by subtype to evaluate for an association with in-breast cancer recurrence by standard versus hypofractionated breast radiation. Dr Frazer Symmans, breast pathologist and expert in this field, will assist with the design and analysis of these future studies using the tumor blocks to be submitted. Final design will depend on the number of blocks collected as well as the number of events.

1.10 Breast-Related Symptoms and Side Effects

We intend to collect patient and physician-reported outcome data for the purpose of further understanding the differences in breast-related symptoms and side effects of hypofractionation compared to conventional fractionation. Our hypothesis is that cosmetic results and breast-related symptoms 3 years after hypofractionated breast radiation with concomitant boost will not be inferior to that obtained 3 years after whole breast irradiation with sequential boost

The Breast Cancer Treatment Outcome Scale (BCTOS) assesses symptoms and side effects associated with breast cancer treatment. This tool is also being used in the RTOG 0413/NSABP B-39 so will facilitate comparisons with the outcomes from this study. The BCTOS is a 22-item measure of perceived aesthetic (e.g., breast shape) and

functional status (e.g., pain, mobility) after breast-conserving surgical treatment (BCT) and radiotherapy (Stanton 2001). This validated scale was assessed in 185 women who underwent BCT and radiotherapy for Stage 0-II disease with 3 months to 18 years of follow-up. The BCTOS produced a factor structure with three internally consistent subscales (i.e., cosmetic status, functional status, and breast specific pain) that demonstrated predictive validity. With patient age, diagnosis duration, and other BCTOS subscales controlled, greater breast specific pain predicted greater depressive symptoms ($P < 0.01$) and lower QOL related to mental health ($P < 0.05$) and physical health ($P < 0.05$). Cosmetic status predicted QOL related to physical health ($P < 0.05$). The relations of breast specific pain with QOL indicators varied somewhat as a function of diagnosis duration.

Physician reported cosmetic outcome will be assessed using a 4 point scale (Harvard/ EORTC). This scale has been used in prior RTOG studies including the ongoing Phase III study (NSABP B-39/RTOG 0413) comparing standard fractionated WBI to PBI.

1.11 Conclusions

Prospective randomized trials have established the principle that hypofractionation may be used for whole breast radiation with acceptable toxicity and equal local control as conventional 50 Gy/ 2 Gy fractionation. However, numerous questions remain to be answered before hypofractionation is accepted for use widely in the United States.

- Phase III trials did not consistently employ a boost so that a three-week fractionation schedule would be reserved for lower risk or elderly patients felt not to require a boost. Given the lack of data on combining hypofractionation with a boost, hypofractionation will not be used in high risk and younger patients in whom a boost is felt to be necessary.
- There may be selection bias against women with larger breast sizes as well since they were not routinely included in hypofractionated trials due to requirements for limitation of dose inhomogeneity in treatment plans.
- There were a relatively low percentage of patients treated with systemic chemotherapy on those trials, which could limit the ability to detect differences in complications with hypofractionation.
- Data on use of a hypofractionated dose schedule with biological equivalence to the cumulative tumor bed dose from the boost is absent from these trials. A sequential boost grafted onto a three-week hypofractionated regimen will only minimally affect the time and cost savings.
- Phase III trials of hypofractionation have not assessed the long-term risk of cardiac toxicity with hypofractionation using NTCP models or long-term clinical follow-up beyond 10 years which is needed to observe differences in cardiac morbidity and mortality.

To address this issue, the American Society of Radiation Oncology convened a task force of experts to make recommendations for fractionation of whole breast irradiation (WBI). After a review of the current literature, there was consensus that hypo-fractionated (HF) WBI is suitable in the following patients: breast cancer patients with pT1-2, N0 disease, >50 years old who do not receive chemotherapy. In regards to boost the task force concluded: “There were few data to define the indications for and toxicity of a tumor bed boost in patients treated with HF-WBI …. The task force agreed that the use of HF-WBI alone (without a boost) is not appropriate when a tumor bed boost is thought to be indicated. When a boost is indicated, there was lack of consensus regarding the appropriateness of HF-WBI (Smith 2010).”

The current study proposes to establish a hypofractionation schedule (with a concurrent boost) that delivers a dose in only 3 weeks that can be applied to a broader patient population than enrolled in the existing hypofractionation studies (high-risk, large breasted, and those requiring chemotherapy) seen routinely in everyday practice. Patient

inclusion criteria will be defined to include patients at higher than average risk for local recurrence who could most benefit from the addition of a tumor bed boost - age < 50 years (even with DCIS), node positive breast cancer, lymphovascular space invasion, presence of an EIC with close (< 2mm) resection margins, focally positive margins, and/or non-hormone sensitive breast cancer. If the proposed regimen were proven to provide equivalent low control even in these higher-risk patients, the impact on the treatment of the majority of breast cancer patients would be practice changing.

The study also develops standards and tests the efficacy (for the first time for breast cancer) of clearly defined anatomic targets (employs the RTOG breast atlas), 3D-conformal external beam radiation therapy and IMRT. NTCP calculations will be used to assess differences in cardiac risk with hypofractionation versus conventional 2 Gy fractionation. Exploratory correlative studies will include genes predictive of outcomes (efficacy and toxicity) related to radiation treatment, and the effects of hypofractionation and IMRT on health economic outcomes.

2.0 OBJECTIVES

2.1 Primary

To determine whether an accelerated course of hypofractionated WBI including a concomitant boost to the tumor bed in 15 fractions following lumpectomy will prove to be non-inferior in local control to a regimen of standard WBI with a sequential boost following lumpectomy for early-stage breast cancer patients.

2.2 Secondary

2.2.1 To determine whether breast-related symptoms and cosmesis from accelerated WBI that is hypofractionated (in only 3 weeks) with a concomitant boost is non-inferior to standard WBI with sequential boost;

2.2.2 To determine whether the risk of late cardiac toxicity in patients with left-sided breast cancer treated with hypofractionation will be non-inferior to conventional fractionated RT based upon analysis of radiation dosimetry from CT-based treatment planning and NTCP calculations;

2.2.3 To determine whether CT-based conformal methods IMRT and 3DCRT for WBI are feasible in a multi-institutional setting following lumpectomy in early-stage breast cancer patients and whether dose-volume analyses can be established to assess treatment adequacy and likelihood of toxicity;

2.2.4 To determine that cosmetic results and breast-related symptoms 3 years after hypofractionated breast radiation with concomitant boost will not be inferior to that obtained 3 years after whole breast irradiation with sequential boost;

2.2.5 To determine whether future correlative studies can identify individual gene expressions and biological host factors associated with toxicity and/or local recurrence from standard and hypofractionated WBI;

2.2.6 If shown to be non-inferior, to then determine if accelerated course of hypofractionated WBI including a concomitant boost to the tumor bed in 15 fractions following lumpectomy will prove to be superior in local control to a regimen of standard WBI with a sequential boost following lumpectomy for early-stage breast cancer patients;

2.2.7 To determine whether treatment costs for hypofractionated WBI with concomitant boost are not higher than that for WBI with sequential boost.

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility (10/21/13)

For questions concerning eligibility, please contact the study data manager

3.1.1 Pathologically proven diagnosis of breast cancer resected by lumpectomy and whole breast irradiation with boost without regional nodal irradiation planned

3.1.2 The patient must be female

3.1.3 The patient must meet at least one of the three following criteria:

A. pStage I, II Breast Cancer AND at least one of the following:

- Age < 50 years or
- Positive axillary nodes or
- Lymphovascular space invasion or
- 2 or more close resection margins (> 0 mm to ≤ 2 mm) or
- 1 close resection margin and extensive intraductal component (EIC) [Per College of American Pathologist (CAP) Recommendation] or
- Focally positive resection margins or
- Non-hormone sensitive breast cancer (ER and PR-negative) or
- Grade III histology or
- Oncotype recurrence score > 25 or

B. pStage 0 breast cancer with nuclear grade 3 DCIS and patient age <50 years or

C. ypStage 0, I, II breast cancer resected by lumpectomy after neoadjuvant systemic therapy

3.1.4 Study entry must be within 50 days from whichever comes later: last surgery (breast or axilla) or last chemotherapy **NOTE**: The day of surgery is Day "0"

3.1.5 If multifocal breast cancer, then it must have been resected through a single lumpectomy incision with negative margins

3.1.6 Breast-conserving surgery with margins defined as follows: (also see 3.1.3 for eligibility)

- Negative margins defined as no tumor at the resected specimen edge.
- Close resection margins > 0 mm to ≤ 2 mm. as follows:
  - One close resection margin and EIC (per College of American Pathologist (CAP) Recommendation)
  - 2 or more close resection margins.
- A focally positive resection margin

3.1.7 **For invasive breast cancer the axilla must be staged by one of the following**:

- Sentinel node biopsy alone (if sentinel node is negative, pN0, pN0$^{(IHC-,+)}$);
- Sentinel node biopsy alone, OR followed by axillary node dissection per investigator discretion, for clinically node negative patients as described below:
  - microscopic sentinel node positive (pN1mic)
  - one or two sentinel nodes positive (pN1) without extracapsular extension
  - negative sentinel node biopsy after neoadjuvant chemotherapy
- Axillary node dissection is required following sentinel node biopsy with a minimum total of 6 axillary nodes if any of the following exist:
  - for > 2 positive SN
  - any positive SN biopsy after neoadjuvant chemotherapy
  - for clinically (by either imaging or examination) T3 disease
  - for extracapsular extension
- Axillary dissection alone (with a minimum of 6 axillary nodes)

3.1.8 Age ≥ 18

3.1.9 CT-imaging of the ipsilateral breast within 28 days prior to study entry for the radiation treatment planning. Must be able to delineate on CT scan the extent of the target lumpectomy cavity for boost

3.1.10 Appropriate stage for protocol entry, including no clinical evidence for distant metastases, based upon the following minimum diagnostic workup:

- History/physical examination, including breast exam (inspection and palpation of the breasts) and documentation of weight and Zubrod Performance Status of 0-2 within 28 days prior to study entry;
- Right and left mammography within 90 days of diagnostic biopsy establishing diagnosis

3.1.11 Patients must have had ER analysis performed on the primary breast tumor prior to study entry according to current ASCO/CAP Guideline Recommendations for hormone receptor testing. If negative for ER, assessment of PgR must also be performed

according to current ASCO/CAP Guideline Recommendations for hormone receptor testing (http://www.asco.org)

3.1.12 CBC/differential obtained within 14 days prior to study entry, with adequate bone marrow function defined as follows:
- Absolute neutrophil count (ANC) ≥ 1,800 cells/mm^3
- Platelets ≥ 75,000 cells/mm^3
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)

3.1.13 Women of childbearing potential must have a negative urine or serum pregnancy test within 14 days of study entry

3.1.14 Women of childbearing potential must be non-pregnant and non-lactating and willing to use medically acceptable form of contraception during radiation therapy

3.1.15 Patient must provide study specific informed consent prior to study entry

3.1.16 Breast implants allowed

3.2 Conditions for Patient Ineligibility (5/6/2013)

3.2.1 AJCC pathologic T4, N2 or N3, M1 pathologic stages III or IV breast cancer

3.2.2 Treatment plan that includes regional node irradiation

3.2.3 Prior invasive non-breast malignancy (except non-melanomatous skin cancer, carcinoma in situ of the cervix) unless disease free for a minimum of 5 years prior to study entry

3.2.4 Prior invasive or in-situ carcinoma of the breast (-prior LCIS is eligible)

3.2.5 Two or more breast cancers not resectable through a single lumpectomy incision

3.2.6 Bilateral breast cancer

3.2.7 DCIS only (without an invasive component) and age ≥ 50 years

3.2.8 DCIS nuclear grade 1 or 2 only (without an invasive component) and age < 50 years

3.2.9 Invasive breast cancer and low risk for 5-year in breast recurrence after lumpectomy with negative margins **that does not meet one of the eligibility factors in 3.1.3.**

3.2.10 Unable to delineate on CT scan the extent of the target lumpectomy cavity for boost (Placement of surgical clips to assist in treatment planning of the boost is strongly recommended, see Section 6.4.2 for details)

3.2.11 Suspicious unresected microcalcification, densities, or palpable abnormalities (in the ipsilateral or contralateral breast) unless biopsied and found to be benign

3.2.12 Non-epithelial breast malignancies such as sarcoma or lymphoma

3.2.13 Paget's disease of the nipple

3.2.14 Male breast cancer

3.2.15 Prior radiotherapy to the breast or prior radiation to the region of the ipsilateral breast that would result in overlap of radiation therapy fields

3.2.16 Intention to administer concurrent chemotherapy for current breast cancer.

3.2.17 Severe, active co-morbidity, defined as follows:
- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
- Transmural myocardial infarction within the last 6 months
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before registration;
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive

3.2.18 Pregnancy or women of childbearing potential who are sexually active and not willing/able to use medically acceptable forms of contraception

3.2.19 Active systemic lupus, erythematosus, or any history of scleroderma, dermatomyositis with active rash

3.2.20 Medical, psychiatric or other condition that would prevent the patient from receiving the protocol therapy or providing informed consent

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility. It is assumed that standard clinical judgment will be used to work-up patients who have physical or laboratory findings suggestive of metastatic disease, and appropriate evaluation will be performed as indicated. Patients with metastatic disease are not eligible for protocol participation.

4.1 Required Evaluations/Management (5/6/2013)

Note: that failure to perform one or more of these tests may result in assessment of a protocol violation.

4.1.1 For patients who have consented to participate in the Cosmesis/Quality of Life portion of the study, forms and photographs must be submitted (see Sections 11.0 and 12.0)

4.1.2 Bone scan (with plain film correlation if needed) for patients with invasive breast cancer when clinically warranted based on symptoms, and either abnormal physical examination, or abnormal (out of the normal reference range of the local site) alkaline phosphatase level within 180 days prior to study entry or within 90 days of last surgery (lumpectomy + axillary surgery) or initiation of neoadjuvant chemotherapy.

4.1.3 CT scans of the chest, abdomen and pelvis, or PET/CT when clinically warranted for patients with invasive breast cancer and new/unusual chest or abdominal symptoms, abnormal physical examination, or abnormal (out of the normal reference range of the local site) liver function tests within 180 days prior to study entry or within 90 days of last surgery (lumpectomy + axillary surgery) or initiation of neoadjuvant chemotherapy.

4.1.4 Chemistry panel that must include AST, ALT, alkaline phosphatase and bilirubin within 14 days prior to study entry

4.2 Recommended Evaluations/Management (5/6/2013)

4.2.1 Bone scan (with plain film correlation if needed) is recommended but not required for patients with positive nodes within 180 days prior to study entry or within 90 days of last surgery (lumpectomy + axillary surgery) or initiation of neoadjuvant chemotherapy

4.2.2 Negative post-excision mammogram for patients with malignancy-associated calcifications after lumpectomy within 180 days prior to study entry

5.0 REGISTRATION PROCEDURES (10/21/13)

Access requirements for OPEN and TRIAD:

Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members' web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.

Note: See below for information on installing TRIAD for submission of digital RT data prior to enrolling patients

5.1 Pre-Registration Requirements for IMRT / 3D-CRT Treatment Approach (10/21/13)

5.1.1 In order to utilize either 3D-CRT or IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements are available on the Imaging and Radiation Oncology Core (IROC) Houston web site. Visit http//irochouston.mdanderson.org and select “Credentialing”.

This study will require each institution to complete a Benchmark case for credentialing. This applies for both the 3D-CRT and IMRT treatment modalities. The Benchmark case is a treatment planning exercise. CT scans for each case will be made available for downloading from the IROC Houston website (http//irochouston.mdanderson.org), and the institution is expected to use this dataset to demonstrate their ability to generate an acceptable dose distribution. The CT datasets will include contours of the breast tissue together with contours of the boost volume. The planning results will be submitted electronically via TRIAD for review. The results of this planning exercise will be examined and approved by the protocol Study Chairs before the first patient can be entered from a particular institution. Upon successful completion and approval of the Benchmark case, IROC Philadelphia will notify the institution that they have completed this requirement.

5.1.2 The institution or investigator must complete a Facility Questionnaire or modify their existing questionnaire (on file at IROC Philadelphia) and send it to IROC Philadelphia for review prior to entering any cases. The Facility Questionnaire can be found at the IROC Houston website (http//irochouston.mdanderson). Updating an existing Facility Questionnaire can be accomplished by contacting: IROC Philadelphia: 215-574-3219.
In order to submit the benchmark credentialing case and all digital data for registered patients, the institution must have an IRB approval. When submitting to TRIAD, select "Clinical Trials (NCI Oncology)", then select "Benchmark" for submission type. IROC Philadelphia will notify the institution when all requirements have been met and the institution is RT credentialed to enter patients onto this study.

5.2 Digital RT Data Submission to RTOG Using TRIAD (10/21/13)

TRIAD, the American College of Radiology's (ACR) image exchange application, will be used for dosimetry digital treatment data.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to Section 5.0 of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. NRG Oncology users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the NRG Oncology/RTOG website Core lab tab.

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

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.3 Regulatory Pre-Registration Requirements (10/21/13)

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

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member web site or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for RTOG 1005 site registration:

Sites must be credentialed for either the IMRT or 3D-CRT Treatment Approaches. Please see protocol section 5.1 for details.

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form (if applicable)

NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the IROC Houston monitoring program. For non-lead group institutions an RT Facilities Inventory From must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

5.3.2 **In addition to the requirements noted above, ALL institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206); study-related regulatory documentation also may be e-mailed to the CTSU at CTSURegulatory@ctsu.coccg.org. This must be done prior to registration of the institution's first case:

- IRB/REB approved consent (English and native language versions*****)
  ***Note**: Institutions must provide certification/verification of IRB/REB consent translation to NRG Oncology Headquarters (described below).
- IRB/REB assurance number renewal information as appropriate.

Non-English Speaking Canadian and Non-North American Institutions
Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG Oncology will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

5.3.3 Pre-Registration Requirements FOR INTERNATIONAL INSTITUTIONS

*For institutions that **do not have an approved LOI** for this protocol:*

International sites must submit an LOI to RTOG Headquarters to receive approval to participate in this trial.
*For institutions that **have an approved LOI** for this protocol:*
All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.4 OPEN Registration (10/21/13)

5.4.1 Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. All site staff will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- See Section 5.0 for obtaining a CTEP-IAM account.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

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

Further instructional information is provided on the open tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org.
For any additional questions contact the CTSU help desk at 1-888-823-5923 or ctsucontact@westat.com.

5.4.2 In the event that the OPEN system is not accessible, participating sites can contact web support for assistance with web registration: websupport@acr.org or call the Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

6.0 RADIATION THERAPY

NOTE: RAPID REVIEWS AND TIMELY REVIEWS ARE REQUIRED. RAPID REVIEWS NEED 3 BUSINESS DAYS FOR PROCESSING. SEE SECTION 6.8.2

This trial is not utilizing the services of the ITC for dosimetry digital treatment data submission. See Section 5.2 for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

NOTE: Please see Appendix V for Contouring Guidelines and Appendix VI for DVH Constraints

NOTE: Radiation therapy must begin within 9 weeks of last surgery or chemotherapy delivery

6.1 Dose Specifications

6.1.1 (Arm I) Standard Whole Breast Irradiation with Sequential Boost

Breast: 50 Gy in 25 fractions of 2 Gy. Optional: 42.7 Gy in 16 fractions of 2.67 Gy
Lumpectomy Cavity: Total dose will be 12 Gy in 6 fractions or 14 Gy in 7 fractions per institutional discretion.

6.1.2 (Arm II) Hypofractionated Whole Breast Irradiation with Concurrent Boost

Breast: 40.0 Gy in 15 fractions of 2.67 Gy fractions per day.
Lumpectomy Cavity: Total dose of 48.0 Gy in 15 fractions of 3.2 Gy fractions per day.

6.2 Technical Factors

6.2.1 The guidelines for IMRT in this trial will conform to the policies set by the Advanced Technology Consortium (ATC) and the National Cancer Institute (NCI) (http://atc.wustl.edu/home/NCI/NCI_IMRT_Guidelines.html)

6.2.2 Each of the target volumes and normal structures listed below must be delineated on each slice from the 3D planning CT in which that structure exists.

6.2.3 Megavoltage photon beams with energies ≥ 6 MV and megavoltage electron beams are required. Proton beams are not allowed.

6.3 Localization, Simulation, and Immobilization

6.3.1 Simulation and treatment may be performed with the patient in the supine or prone position.

6.3.2 Patients should be optimally positioned with alpha cradle casts, breast boards, wing boards and/ or other methods of immobilization at the discretion of the treating physician.

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

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

6.3.5 A treatment planning CT scan in the treatment position will be required to define the clinical target volumes (CTV) and planning target volumes (PTV).

- The CT required for generation of a virtual plan with 3DCRT or IMRT must be post-lumpectomy
- Radio-opaque markers must be placed on external landmarks at the acquisition of the CT scan to facilitate contouring segmentation of the CT data-set. These markers should identify: 1) The lumpectomy incision 2) The outline of the palpable breast tissue circumferentially at least from 2 o'clock to 10 o'clock 3) The superior border of the breast tissue at 12 o'clock based on palpation. Additional markers to define the borders of "clinical" tangent fields (e.g. based on the palpable breast tissue and boney landmarks) are often helpful.
- The CT should extend cephalad to start at or above the mandible and extend sufficiently caudally (or inferiorly) to the inframammary fold to encompass the entire lung volume. A CT scan image thickness of ≤ 0.5 cm should be employed.

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

6.3.7 For obese patients: while every effort should be made to include the full external contour in the planning CT, it is permissible to use CT with cutoff of a portion of the body image due to the limited field-of-view of the CT scanner only if: (1) the treated breast is fully included in the CT, (2) no treatment beam goes through the cutoff portion, and (3) maximum doses in cutoff normal structures (e.g., contralateral lung, contralateral breast) can still be evaluated.

6.4 Treatment Planning/Target Volumes (10/21/13)

6.4.1 The definitions for the CTV, PTV and normal structures used in this protocol generally conform to the RTOG-endorsed consensus guidelines for delineation of target and normal structures for breast cancer (http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx) and the 1993 ICRU report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

6.4.2 Target Volumes and Normal Structures

Lumpectomy volumes:

Lumpectomy GTV: Contour using all available clinical and radiographic information including the excision cavity volume, architectural distortion, lumpectomy scar, seroma and/or extent of surgical clips (clips are strongly recommended). Patients without a clearly identifiable lumpectomy bed are not eligible for protocol participation.

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

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

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

Breast volumes:

Breast CTV. Includes the palpable breast tissue demarcated with radio-opaque markers at CT simulation (see section 6.3), the apparent CT glandular breast tissue visualized by CT, consensus definitions of anatomical borders, and the Lumpectomy CTV from the breast cancer atlas (section 6.4). The breast CTV is limited anteriorly within 5 mm from the skin and posteriorly to the anterior surface of the pectoralis, serratous anterior muscle excluding chestwall, boney thorax and lung. In general, the pectoralis and/or serratous anterior muscles are excluded from the breast CTV unless clinically warranted by the patient's pathology. The breast CTV should generally follow consensus guidelines (http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.asp)

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

Breast PTV Eval: Since a substantial part of the Breast PTV often extends outside the patient, the Breast PTV is then copied to a Breast PTV Eval which is

edited. This Breast PTV Eval is limited anteriorly to exclude the part outside the patient and the first 5 mm of tissue under the skin (in order to remove most of the build up region for the DVH analysis) and posteriorly is limited no deeper to the anterior surface of the ribs (excludes boney thorax and lung). This Breast PTV Eval is the structure used for DVH constraints and analysis. This Breast PTV Eval cannot be used for beam aperture generation.

Contralateral breast

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

- *Posterior border*: At the anterior surface of the pectoralis, serratous anterior muscles excluding chestwall, ribs, boney thorax and lung/heart;
- *Medial border:* The sternal-costal junction,
- *Lateral border*: Varies based on the size of the breast but typically is at the mid-axillary line and excludes the ipsilateral lattismus dorsi muscle.
- *Cephald border*: Should be similar to that of the ipsilateral breast CTV
- *Caudal border*: Inframammary fold and 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.

Refer to the breast contouring atlas:
http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx

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

Contralateral lung. This 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.

6.4.3 Treatment Planning

CT-based planning with tissue inhomogeneity correction is required

IMRT or 3D-CRT are permitted

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 and apertures to meet the target and critical structure dose-volume constraints.

2. The 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 defined in (1) above should deliver > 50% of the total number of monitor units for the beam orientation.

4. Simultaneous integrated boost to deliver whole breast and boost doses at the same time with IMRT is allowed in ARM II.

5. If an IMRT plan is used with another IMRT plan, forward-planning photon beams, and/or electron beam, the 3D composition dose distribution and DVHs should be generated.

6. 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.

7. 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.

8. 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 3D-CRT 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 3D-CRT plans. These forward-planned or segmental treatment techniques are those intended to mainly 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.

Whole Breast Radiation Therapy

The breast PTV is used to generate the beam apertures with an additional margin to take into account penumbra. Fields should include all of the breast PTV and boost PTV. The aperture margin generally needed beyond the PTV is 5 mm. The goals of treatment planning are to encompass the breast PTV and minimize inclusion of the heart and lung.

Field arrangements for 3D conformal and IMRT of the Breast PTV are at the 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 Breast PTV and normal tissues outlined below

Boost Radiation Therapy

The lumpectomy boost may be given by either electron beam or photon beams using either 3D-CRT or IMRT. A composite dose distribution and DVHs that include whole breast irradiation using either IMRT or 3D-CRT and lumpectomy cavity boost using electron beams, IMRT or 3D-CRT must be provided for review. Simultaneous integrated boost using IMRT is allowed in ARM II.

Boost radiation must be planned from the initial CT for radiation planning. Changes in patient positioning for the boost are not allowed. The table position may move to optimize electron beam radiation.

Brachytherapy boost is not allowed.

In Arm I the boost will begin without a treatment break after completion of the treatment to the entire breast.

If electron boost is used, there must be adequate dosimetric coverage of the lumpectomy PTV eval.

Field arrangements for 3D-CRT and IMRT boosts are at the 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 Lumpectomy PTV and normal tissues as outlined below.

Treatment plans must meet Dose Volume Constraints (Section 6.4.3) for the contoured targets and normal structures (Section 6.4.2). Various treatment approaches may be used to develop treatment plans and a composite plan combining WBI and boost plans must be generated.

a. Approaches for ARM 1 Standard Whole Breast Irradiation (WBI) with sequential boost include:
i. 3DCRT WBI with 3DCRT sequential boost
ii. 3DCRT WBI with IMRT sequential boost
iii. 3DCRT WBI with electron sequential boost
iv. IMRT WBI with 3DCRT sequential boost
v. IMRT WBI with IMRT sequential boost
vi. IMRT WBI with electron sequential boost

b. Approaches for ARM 2 Hypofractionated Whole Breast Irradiation with concurrent boost include:
vii. 3DCRT WBI with 3DCRT concurrent boost
viii. 3DCRT WBI with IMRT concurrent boost
ix. 3DCRT WBI with electron concurrent boost
x. IMRT WBI with 3DCRT concurrent boost
xi. IMRT WBI with IMRT concurrent boost
xii. IMRT WBI with electron concurrent boost
xiii. IMRT WBI with IMRT simultaneously integrated boost (SIB)

NOTE: For Approach xiii (SIB), only one plan integrating both WBI and boost is generated. For all other approaches, two plans (one for WBI and another for boost) are generated

Dose-volume histogram (DVH) analysis is required
(See Appendix VI for summary table of dose volume constraints)

For both ARM I and ARM II, the treatment plan for the whole breast and boost must be done prior to the start of radiation and meet the following dose-volume constraints defined below.
All maximum doses should be defined in one dose calculation voxel, e.g., 3x3x3 mm^3.
The conformity index is an optional constraint, but must be recorded and reported on all cases. All submitted DVHs will be evaluated for compliance with these parameters:

ARM I Standard Whole Breast Irradiation with Sequential boost

Breast PTV Eval:

- Per Protocol: At least 95% of the breast PTV Eval will receive at least 95% (47.5 Gy) of the whole breast prescribed dose of 50 Gy (or 40.6 Gy if hypofractionation whole breast fractionation used).
  Variation Acceptable: At least 90% of the breast PTV Eval will receive at least 90% (45 Gy) of the whole breast prescribed dose of 50 Gy (or 38.4 Gy if hypofractionation whole breast fractionation used).
- Per Protocol: No more than 30% of the breast PTV Eval will exceed 100% of the boost prescribed dose of 62-64 Gy (or 54.7-56.7 Gy if hypofractionated whole breast fractionation used).
  Variation Acceptable: No more than 35% of the breast PTV Eval will receive ≥ 100% of the boost prescribed dose of 62-64 Gy (or 54.7-56.7Gy if hypofractionated whole breast fractionation used).
- Per Protocol: No more than 50% of the volume of breast PTV Eval will exceed 54 Gy (or exceed 46.1 Gy if hypofractionated whole breast fractionation used).
  Variation Acceptable: No more than 50% of the volume of breast PTV Eval will exceed 56 Gy (or exceed 47.8 Gy if hypofractionated whole breast fractionation used).
- Per Protocol: The maximal point dose will not exceed 115% of the prescription whole breast dose, e.g. will not exceed 57.5 Gy for a prescribed dose of 50 Gy or will not exceed 49.1 Gy for a prescribed dose of 42.7 Gy if hypofractionation whole breast fractionation is used.
  Variation Acceptable: The maximal point dose will not exceed 120% (will not exceed 60 Gy for a prescription whole breast dose of 50 Gy or will not exceed 51.2 Gy if hypofractionated 42.7 Gy is used. The maximal dose may be evaluated without boost fields.
- Optional constraint: Conformity Index (CI): defined as “the ratio of the volume covered by the 95% prescription isodose over the volume of Breast PTV Eval.
  Per Protocol: CI is no less than 0.95 and no more than 2.0.
  Variation Acceptable: CL is no less than 0.85 and no more than 2.5.

Lumpectomy PTV Eval:

- Per Protocol: At least 95% of the Lumpectomy PTV Eval will receive at least 58.9-60.8 Gy which is 95% of the cumulative boost prescribed dose of 62-64 Gy (or at least 52-53.9 Gy which is 95% of 54.7-56.7 Gy if hypofractionated whole breast fractionation used).
  Variation Acceptable: At least 90% of the Lumpectomy PTV Eval will receive at least 55.8— 57.6 Gy which is 90% of the cumulative boost prescribed dose of 62-64 Gy (or at least 49.2-51 Gy which is 90% of 54.7-56.7 Gy if hypofractionated whole breast fractionation used).
- Per Protocol: No more than 5% of the Lumpectomy PTV Eval will exceed 68.2-70.4 Gy which is 110% of the boost prescribed dose of 62-64 Gy (or

exceed 60.2-62.4 Gy which is 110% of 54.7-56.7 Gy if hypofractionated whole breast fractionation used).

Variation Acceptable: No more than 10% of the Lumpectomy PTV Eval will exceed 68.2-70.4 Gy which is 110% of the boost prescribed dose of 62-64 Gy (or exceed 60.2-62.4 Gy which is 110% of 54.7-56.7 Gy if hypofractionated whole breast fractionation is used).

- Per Protocol: The maximal point dose will not exceed 71.3-73.6 Gy which is 115% of the boost prescribed dose of 62-64 Gy (or will not exceed 62.9-65.2 Gy which is 115% of 54.7-56.7 Gy if hypofractionated whole breast fractionation is used).

  Variation Acceptable: The maximal dose point is will not exceed 74.4-76.8 Gy which is 120% of the boost prescribed dose of 62-64 Gy (or maximal dose will not exceed 65.6-68 Gy which is 120% of 42.7 if hypofractionation is used).
- Optional constraint: Conformity Index (CI): defined as "the ratio of the volume covered by the 95% prescription isodose over the volume of lumpectomy PTV Eval. Per Protocol: CI is no less than 0.95 and no more than 2.5.

  Variation Acceptable: CL is no less than 0.9 and no more than 3

Contralateral Breast

- Per Protocol: The maximum dose to contralateral breast does not exceed 310 cGy and no more than 5% exceeds 186 cGy.

  Variation Acceptable**:** The maximum dose does not exceed 496 cGy and no more than 5% exceeds 310 cGy

Ipsilateral Lung

- Per Protocol**:** No more than 15% of the ipsilateral lung exceeds 20 Gy.

  Variation Acceptable**:** No more than 20% of the ipsilateral lung exceeds 20 Gy.
- Per Protocol**:** No more than 35% of the ipsilateral lung exceeds 10 Gy.

  Variation Acceptable**:** No more than 40% of the ipsilateral lung exceeds 10 Gy.
- Per Protocol**:** No more than 50% of the ipsilateral lung exceeds 5 Gy.

  Variation Acceptable**:** No more than 55% of the ipsilateral lung exceeds 5 Gy.

Contralateral Lung

- Per Protocol**:** No more than 10% of the contralateral lung exceeds 5 Gy.

  Variation Acceptable: No more than 15% of the contralateral lung exceeds 5 Gy

Heart

- Per Protocol**:** No more than 5% of the whole heart exceeds 20 Gy for left-sided breast cancers and 0% of the heart exceeds 20 Gy for right-sided breast cancers.

  Variation Acceptable**:** No more than 5% of the whole heart exceeds 25 Gy for left-sided breast cancers, and 0% of the heart exceeds 25 Gy for right-sided breast cancers.
- Per Protocol**:** No more than 30% of the whole heart exceeds 10 Gy for left sided breast cancers and no more than 10% of the heart exceeds 10 Gy for right-sided breast cancers.

  Variation Acceptable: No more than 35% of the whole heart exceeds 10 Gy for left-sided breast cancers and no more than 15% of the heart exceeds 10 Gy for right-sided breast cancers.
- Per Protocol**:** The mean heart dose does not exceed 400 cGy.

  Variation Acceptable**:** The mean heart dose does not exceed 500 cGy.

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

Thyroid

ARM 1 if prescribed 62-64 Gy:

- Per Protocol**:** The maximum point dose does not exceed 2% of the prescribed dose (Maximum point dose does not exceed1.24-1.28 Gy).
  Variation Acceptable**:** The maximum point dose does not exceed 3% of the prescribed dose (Maximum point dose does not exceed 1.86-1.92 Gy).
  .

ARM 1 if prescribed 54.7-56.7 Gy:

- Per Protocol**:** The maximum point dose does not exceed 2% of the prescribed dose (Maximum point dose does not exceed 1.09-1.13 Gy).
  Variation Acceptable**:** The maximum point dose does not exceed 3% of the prescribed dose (Maximum point dose does not exceed 1.64-1.70 Gy

ARM II Hypofractionated Whole Breast Irradiation with Concomitant Boost

Breast PTV Eval

- Per Protocol**:** At least 95% of the breast PTV Eval will receive at least 95% (38 Gy) of the whole breast prescribed dose of 40 Gy.
  Variation Acceptable**:** At least 90% of the breast PTV Eval will receive at least 90% (36 Gy) of the whole breast prescribed dose.
- Per Protocol**:** No more than 30% of the breast PTV Eval will exceed 100% of the boost prescribed dose of 48 Gy.
  Variation Acceptable**:** No more than 35% of the breast PTV Eval will exceed 100% of the boost prescribed dose of 48 Gy.
- Per Protocol**:** No more than 50% of the volume of breast PTV Eval will exceed 43.2 Gy.
  Variation Acceptable**:** No more than 50% of the volume of breast PTV Eval will exceed ≥ 44.8 Gy
- Per Protocol**:** The maximal point dose will not exceed 115% (which is 46 Gy) of the whole breast prescribed dose of 40 Gy.
  Variation Acceptable**:** The maximal point dose will not exceed 120% (which is 48 Gy) of the whole breast prescribed dose of 40 Gy.
  For simultaneously integrated boost, acceptability on the maximum dose in breast_PTVeval [i.e., not exceeding 46Gy per protocol or not exceeding 48 Gy variation acceptable] should be judged that no disconnected isodose lines of 48 Gy are seen in the regions outside the lumpectomy PTV. In other words, it is acceptable if no isolated hot spots of more than 48 Gy are found in the regions outside the lumpectomy PTV. For all other treatment options, the maximum dose may be evaluated by turning off the boost fields.
- Optional constraint: Conformity Index (CI): defined as “the ratio of the volume covered by the 95% prescription isodose over the volume of Breast PTV Eval.
  Per Protocol: CI is no less than 0.95 and no more than 2.0.
  Variation Acceptable: CI is no less than 0.85 and no more than

Lumpectomy PTV Eval

- Per Protocol**:** At least 95% of the Lumpectomy PTV Eval will receive at least 95% (at least 45.6 Gy) of the boost prescribed dose of 48 Gy.
  Variation Acceptable**:** At least 90% of the Lumpectomy PTV Eval will receive at least90% (43.2 Gy) of the boost prescribed dose of 48 Gy.
- Per Protocol**:** No more than 5% of the Lumpectomy PTV Eval will exceed 110% (will not exceed 52.8 Gy) of the boost prescribed dose of 48 Gy.
  Variation Acceptable**:** No more than 10% of the Lumpectomy PTV Eval will exceed 110% (will not exceed 52.8 Gy) of the boost prescribed dose of 48 Gy.
- Per Protocol**:** The maximal point dose will not exceed 115% (will not exceed55.2 Gy) of the boost prescribed dose of 48 Gy.

Variation Acceptable**:** The maximal point dose will not exceed 120% (will not exceed 57.6 Gy).

- Optional constraint: Conformity Index (CI): defined as "the ratio of the volume covered by the 95% prescription isodose over the volume of lumpectomy PTV Eval. Per Protocol**:** CI is no less than 0.95 and no more than2.5.
  Variation Acceptable**:** CI is no less than 0.9 and no more than 3

Contralateral Breast

- Per Protocol: The maximum dose to contralateral breast does not exceed 240 cGy and no more than 5% exceeds 144 cGy.
  Variation Acceptable: The maximal dose to contralateral breast does not exceed384 cGy and no more than 5% exceeds 240cGy.

Ipsilateral Lung

- Per Protocol: No more than 15% of the ipsilateral lung exceeds 16 Gy.
  Variation Acceptable: No more than 20% of the ipsilateral lung exceeds 16 Gy.
- Per Protocol**:** No more than 35% of the ipsilateral lung exceeds 8 Gy.
  Variation Acceptable**:** No more than 40% of the ipsilateral lung exceeds 8 Gy.
- Per Protocol**:** No more than 50% of the ipsilateral lung exceeds 4 Gy.
  Variation Acceptable**:** No more than 55% of the ipsilateral lung exceeds 4 Gy.
- Contralateral Lung
- Per Protocol: No more than 10% of the contralateral lung exceeds 4 Gy.
  Variation Acceptable**:** No more than 15% of the contralateral lung exceeds 4 Gy.

Heart

- Per Protocol**:** No more than 5% of the whole heart exceeds 16 Gy for left-sided breast cancers, and 0% of the heart exceeds 16 Gy for right-sided breast cancers.
  Variation Acceptable**:** No more than 5% of the whole heart exceeds 20 Gy for left-sided breast cancers, and 0% of the heart exceeds 20 Gy for right-sided breast cancers.
- Per Protocol: No more than 30% of the whole heart exceeds 8 Gy for left sided breast cancers and no more than 10% of the heart exceeds 8 Gy for right-sided breast cancers.
  Variation Acceptable**:** No more than 35% of the whole heart exceeds 8 Gy for left-sided breast cancers and no more than 15% of the heart exceeds 8 Gy for right-sided breast cancers.
- Per Protocol**:** The mean heart dose does not exceed 320 cGy.
  Variation Acceptable**:** The mean heart dose does not exceed 400 cGy.

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

Thyroid

- Per Protocol**:** The maximum point dose does not exceed 2% of the prescribed dose (Maximum point dose does not exceed 0.96 Gy).
  Variation Acceptable**:** The maximum point dose does not exceed 3% of the prescribed dose (Maximum point dose does not exceed 1.44 Gy).

Skin bolus is not allowed.

6.5 Critical Structures (10/21/13)

Note: All required structures must be labeled for digital RT data submission as listed below in the table. Resubmission of data may be required if labeling of structures does not conform to the standard dicom name listed.

The following table outlines the naming of the various normal and critical structures for submission to TRIAD:

Standard Name	***Description***
BREAST_CNTR	Contralateral breast
SURG_BED	Surgical bed
CTV_WB	CTV for the whole breast volume
HEART	Heart
LUNG_IPSI	Ipsilateral Lung
LUNG_CNTR	Contralateral Lung
PTV_WB	PTV for whole breast
PTV_WB_EVAL	PTV volume used to evaluate coverage
SKIN	External Patient Contour
THYROID	Thyroid
BREAST_IPSI	Ipsilateral Breast
CTV_SURG_BED	CTV for the Surgical Bed Volume
PTV_SURG_BED	PTV Surgical Bed for CTV growth
PTV_SURG_BED_EVAL	PTV volume used to evaluate coverage

6.6 Treatment Verification

6.6.1 Before first treatment

Portal films or images of each 3DCRT beam and an orthogonal pair for all patients must be obtained and approved by a physician prior to initiation of treatment.

6.6.2 Subsequent images or films

Subsequent treatment images may be obtained every fraction. At the minimum, orthogonal pair films or treatment images must be obtained prior to fraction number 5 and every 5 fractions subsequently. The imaging modality and process should be performed based on the institutional guidelines.

6.7 Documentation Requirements (10/21/13)

All films or images are to be maintained at the local facility. (Please refer to Section 12.2 for data submission)

6.8 Compliance Criteria (5/11/12)

DVHs for the breast PTV Eval and lumpectomy PTV Eval and designated normal structures will be compared to determine protocol compliance according to the following rules:

6.8.1 Per Protocol**:** All specified DVH requirements identified as IDEAL in Section 6.4.3 have been met.

6.8.2 Variation Acceptable**:** Specified DVH requirements in Section 6.4.3 between Ideal and Acceptable.

6.8.3 Deviation Unacceptable**:** Specified DVH requirements for Variation Acceptable in Section 6.4.3 are not met.

6.8.4 Treatment Interruption (elapsed/break days);

Treatment interruptions should be clearly documented in the patient's medical record:

Per Protocol: No breaks except weekends and holidays.
Acceptable variation: Arm 1 1-10 days, Arm 2 1- 5 days:
Unacceptable variation: Arm 1 > 10 days, Arms 2 > 5 days.

6.9 R.T. Quality Assurance Reviews (10/21/13)

6.9.1 Each case will be submitted digitally to TRIAD where it will be processed and made available for review by study chairs or designees

6.9.2 Review Process for Arm I Standard Whole Breast Irradiation with Sequential Boost

The first 3D-CRT case and the first IMRT case enrolled by each radiation oncology facility will undergo timely review. In this process, the finalized treatment plan is electronically submitted and reviewed. Each of these cases may proceed to treatment following planning without waiting for review and approval. Treatment plans must be submitted within one week of treatment initiation. These cases will be reviewed in a timely manner with feedback given to the submitting radiation oncology facility. Corrections and resubmission of data will be requested for cases that do not meet contouring and quality assurance criteria.

6.9.3 Review Process for Arm II Hypofractionated Whole Breast Irradiation with Concomitant Boost

Rapid Review

The first 3D-CRT case and the first IMRT case enrolled onto the trial from each radiation oncology facility will undergo rapid review. In this process, the finalized treatment plan must be electronically submitted, reviewed, and approved prior to the start of treatment. Additional patients may not be enrolled until approval from the rapid review case is received. Allow 3 business days for the results of the rapid review process. Cases that are submitted on a Friday will not be processed until the following Monday. The rapid review process will not start until all required data is received by the IROC Philadelphia. Cases that do not meet contouring and quality assurance criteria will not be approved and corrections will need to be made to obtain approval for accrual and treatment. If corrections or additional documentation is requested, the subsequent submission of the case will be given priority review.

Timely Review

After the first 3D-CRT and IMRT cases are submitted for rapid review, the subsequent first 3 cases of 3D-CRT and the first 3 cases of IMRT from each radiation oncology facility will undergo a timely review. Each of these cases may proceed to treatment following planning without waiting for review and approval. The treatment plan must be submitted within one week of treatment initiation. These cases will be reviewed in a timely manner with feedback given to the submitting radiation oncology facility. Corrections and resubmission of data will be requested for cases that do not meet contouring and quality assurance criteria.

Feedback regarding treatment guideline compliance will be forwarded to the radiation oncology facility. During the period of timely review, the radiation oncology facility will be permitted to continue accrual. If the review of cases 3 or 4 demonstrates a treatment plan that is unacceptable, the radiation oncology facility will be required to repeat the rapid review and timely review process. Additional patients may not be enrolled until approval for the rapid review case is received**.**

6.9.4 Review of all IMRT and 3DCRT conformal cases

All cases enrolled on trial will be reviewed, including those submitted after successful completion of the rapid/timely review process. Corrections and resubmission of data will be requested for cases that do not meet contouring and quality assurance criteria. If protocol non-compliance is documented at any time subsequent to completing the timely review process, the radiation oncology facility will be required to repeat the timely review process and successfully complete planning of (3 consecutive cases) in order for the facility is to continue enrollment. *The radiation oncology facility will be permitted to continue accrual.*

6.9.5 The Radiation Oncology Chairs Frank Vicini, MD, Gary Freedman, MD, Julia White, MD, and Douglas Arthur, MD will perform an RT Quality Assurance Review on all cases enrolled on an ongoing basis. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at IROC Philadelphia, whichever occurs first. These

reviews will be on going and performed at the NRG Oncology semi-annual meetings as well as at IROC Philadelphia.

6.10 Radiation Therapy Adverse Events

6.10.1 All Radiation Therapy AEs will be scored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4

6.10.2 Short Term

Fatigue is an anticipated systemic reaction to radiation treatment. Skin erythema, desquamation, breast edema, breast tenderness and myositis are potential local reactions.

6.10.3 Long Term

Long term effects possibly include radiation pneumonitis, rib fractures, and for left-sided lesions cardiac complications

6.11 Radiation Therapy Adverse Event Reporting (4/4/14)

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event (AE) reporting. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP-AERS (CTEP Adverse Event Reporting System) application accessed via the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613).

6.11.1 Adverse Events (AEs) and Serious Adverse Events (SAEs) Reporting Requirements

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm] Routine adverse event reporting guidelines are available at: (http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx).

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.
- Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner

Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table below will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below. **Contact the CTEP-AERS Help Desk if assistance is required.**

CTEP-AERS REPORTING REQUIREMENTS

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the Adverse Event Expedited Reporting System, accessed via the CTEP web site, **https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613**

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy (RT)-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.
In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to NRG Oncology by phone, (1-800-227-5463, and ext.4189). An electronic report must be submitted immediately upon re-establishment of the Internet connection.

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation the NRG Oncology dedicated SAE FAX, 215-717-0990**.**
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS System as “expedited reporting NOT required” must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the “NOT Required” assessment; the CTEP-AERS System allows submission of all reports regardless of the results of the assessment.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies within 30 Days of the Last Administration of Intervention [1, 2]

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

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

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

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

Expedited 24-hour notification followed by complete report within 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

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

Effective Date: May 5, 2011

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

The following are exceptions to expedited reporting: grade 1 and grade 2 adverse events. Routine AE reporting processes fulfill safety reporting obligations for these events.

6.11.2 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

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 via CDUS unless otherwise specified.

7.0 DRUG THERAPY (5/11/2012)

7.1 Chemotherapy

Chemotherapy may be given at the discretion of the patient's medical oncologist. The use of chemotherapeutic agents during radiation therapy is not allowed. Chemotherapy is permitted both as an adjuvant or neoadjuvant to surgery. All adjuvant chemotherapy will be given prior to radiotherapy. Initiation of radiotherapy should be at least 2 weeks after the last cycle of adjuvant chemotherapy.

7.2 Hormonal Therapy

Patients with ER-positive and / or PR-positive tumors should be treated with hormonal therapy for a minimum of 5 years. The dose and schedule of the drug(s) should be consistent with the instructions in the drug package inserts. Hormonal therapy may be initiated before, during or after completion of radiotherapy at the discretion of the investigator.

7.3 Trastuzumab

Trastuzumab or other anti-HER2 agent is permitted at the investigator's discretion for patients whose tumors are HER2 positive. The dose and schedule of these agents should be per standard treatment protocol. The use of Trastuzumab during radiotherapy is permitted.

8.0 SURGERY (5/11/2012)

Oncoplastic surgery is permitted as long as clear definition of the surgical cavity by clips or by postoperative changes at CT treatment planning is achievable.

9.0 OTHER THERAPY (5/11/2012)

9.1 Permitted Therapies

9.1.1 Anti endocrine therapy (Tamoxifen, aromatase inhibitors, etc.) are allowed at any time (see Section 7.2)

9.1.2 Chemotherapy (see Section 7.1)

9.1.3 Targeted therapy (trastuzumab) (see Section 7.3)

9.1.4 Oncoplastic breast conserving surgery (see Section 8.0)

9.2 Non-permitted Therapies

9.2.1 The use of chemotherapeutic agents during radiation therapy is not allowed.

10.0 TISSUE/SPECIMEN SUBMISSION

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission or cosmesis/quality of life assessment. If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission

The NRG Oncology Biospecimen Bank at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue. The NRG Oncology Biospecimen Bank provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The NRG Oncology Biospecimen Bank also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis.

In this study, tissue will be submitted to the NRG Oncology Biospecimen Bank for the purpose of tissue banking and future translational research.

Future correlative studies for this trial include a plan to genotype subjects for selected genes for which an association with the development of normal tissue toxicity in breast cancer radiotherapy patients has been identified (see Introduction section 1.9.1 for rationale and examples). Future correlative studies for this protocol also include plans for an analysis by subtype as determined by gene expression analysis (see section 1.9.2). The goal is to evaluate for an association with subtype and in-breast cancer recurrence by standard versus hypofractionated breast radiation.

The final design of these studies will depend on the number of specimens collected; the number of events observed in the trial, the state of scientific knowledge and the capability of the technology available at the time accrual to the trial is complete. Future correlative studies will be submitted for separate scientific and institutional review board review before they are implemented.

10.2 Specimen Collection for Tissue Banking and Translational Research (10/21/13)

For patients who have consented to participate in the tissue/blood component of the study.

The following must be provided in order for the case to be evaluable for the NRG Oncology Biospecimen Bank:

10.2.1 One H&E stained slide of the tumor (this must be either the invasive portion of the tumor and/or the grade 3 DCIS portion if no invasive component;(slide can be a duplicate cut stained H&E; it does not have to be the diagnostic slide).

- A corresponding paraffin-embedded tissue block (preferred) of the tumor or a 2 mm diameter core of tumor tissue punched from the tissue block containing the invasive tumor (or the grade 3 DCIS if no invasive tumor present) with a punch tool and submitted in a plastic tube labeled with the surgical pathology number and block ID. The block or punches must be submitted with the H&E from the same block.
  NOTE: A kit with the punch, tube, and instructions can be obtained free of charge from the Biospecimen Resource. Block or core must be clearly labeled with the pathology identification number and block ID that corresponds to the Pathology Report.
  NOTE: If sites are unable to submit a block or punch from the block then they may instead submit 1 H&E and 10-15 unstained slides from the tumor block. The unstained slides must be cut from the same block as the H&E and must be labeled with the pathology number and block ID.
- If available, a corresponding paraffin-embedded tissue block (preferred) of normal breast tissue taken from adjacent to tumor (or a 2 mm diameter core of this tissue punched from the tissue block containing the normal with a punch tool and submitted in a plastic tube labeled with the surgical pathology number). **NOTE:** A kit with the punch, tube, and instructions can be obtained free of charge from the NRG Onoclogy Biospecimen Bank. Block or core must be clearly labeled with the pathology identification number and block ID that corresponds to the Pathology Report.
  NOTE: If sites are unable to submit a block or punch from the block then they may instead submit 1 H&E and 10-15 unstained slides from the normal tissue block. The unstained slides must be cut from the same block as the H&E and must be labeled with the pathology number and block ID

10.2.2 A Pathology Report documenting that the submitted block or core contains tumor. The report must include the NRG ONcology protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.2.3 A Specimen Transmittal Form clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Bank; if for translational research, this should be stated on the form. The form must include the NRG Oncology protocol number and patient's case number.

Plasma and whole blood collection: For detailed processing and shipping instructions, see Appendix IV.

10.2.4 Plasma and Whole Blood for Tissue Banking

The following materials must be provided to the NRG Oncology Biospecimen Bank: A Specimen Transmittal Form documenting the date of collection of the biospecimen; the NRG Oncology protocol number, the patient's case number, time point of study, and method of storage, for example, stored at -80° C, must be included. The specimens to be provided are:

- 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) taken from patient and processed for collection of plasma. This sample is to be obtained only once prior to treatment. No additional samples are to be obtained during follow-up visits following treatment.
- 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) taken from patient for collection of DNA. This sample is to be obtained once prior to treatment. However, if the site missed this collection time point, they may collect whole blood at any time point or during a follow-up visit. No additional samples are to be obtained.

10.2.5 Storage Conditions

Store frozen biospecimens at -80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on Specimen Transmittal Form the storage conditions used and time stored

10.2.6 Specimen Collection Summary

Specimens for Tissue Banking/Translational Research			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary tumor (this must be either the invasive portion of the tumor and/or the grade 3 DCIS portion if no invasive component).	Prior to protocol treatment	H&E stained slide Pre-treatment	Slide shipped ambient
A corresponding paraffin-embedded tissue block (preferred) of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a punch tool	Prior to protocol treatment	Paraffin-embedded tissue block or punch biopsy (must match the H&E slide being submitted) Note: For sites unable to submit the block or punch then 10-15 unstained slides is an acceptable substitute	Block or punch shipped ambient
If available: representative H&E stained slides of Normal tissue adjacent to the tumor (>1cm from lesion)	Prior to protocol treatment	H&E stained slide Pre-treatment	Slide shipped ambient
If available: A paraffin-embedded tissue block of adjacent normal tissue (>1cm from lesion) taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a punch tool	Prior to protocol treatment	Paraffin-embedded tissue block or punch biopsy Note: For sites unable to submit the block or punch then 10-15 unstained slides is an acceptable substitute	Block or punch shipped ambient
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA	Prior to protocol treatment	Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials	Plasma sent frozen on dry ice via overnight carrier (Mon-Wed)

tube#1(purple/lavender top) and centrifuge		(five to ten)	
Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Prior to protocol treatment. (**Note**: If site missed this collection time point they may collect whole blood for DNA at any time point or follow up visit but must note this on the ST).	Frozen whole blood samples containing 1ml per aliquot in 1 mL cryovials (three to five)	Whole blood sent frozen on dry ice via overnight carrier (Mon-Wed)

10.2.7 Submit materials for Tissue Banking and Translational Research as follows:

U. S. Postal Service Mailing Address: <u>For Non-frozen Specimens Only</u>
NRG Oncology Biospecimen Bank
University of California San Francisco
UCSF Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): <u>For Trackable FFPE and ALL Frozen Specimens</u>
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
Questions: 415-476- 7864/FAX 415-476-5271; RTOG@ucsf.edu

10.3 Reimbursement (4/4/14)

Please note that with the start of the new NCI National Clinical Trials Network (NCTN) Program, NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the new NCTN Program. This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system. OPEN will serve as the registration system for all patient enrollments onto NCI-sponsored NCTN trials, including this study, which will be transitioned into the new Program from the NCI-sponsored Cooperative Group Clinical Trials Program.

10.4 Confidentiality/Storage

(See the Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

10.4.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient's case number only. The NRG Oncology Biospecimen Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.4.2 Specimens for tissue banking will be stored for an indefinite period of time. Trial participants will be invited to donate specimens for tissue banking and to consent to store these indefinitely for future translational studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS (5/6/2013)

11.1 Study Parameters

See Appendix I for a summary of assessments and time frames. Note: Clarifications of or exceptions to the study parameters are indicated in Appendix I with an asterisk (*) and are discussed below:

11.1.1 A breast assessment will be conducted weekly during radiation and at the last day of radiation. This assessment will include inspection of the breast being treated and toxicity assessment. Palpation of the breast during this assessment is optional at the discretion of the treating physician.

11.1.2 A breast examination will be conducted within 28 days prior to study entry, at 1 month, at 6 months and subsequent interval visits where the history and physical examination is required. An examination is inspection and palpation of both breasts and toxicity assessment

11.2 Cosmetic and Quality of Life Outcomes (1/9/14)

NOTE: Non-chemotherapy Cosmesis subset closed to accrual 3/8/13; chemotherapy Cosmesis subset closed to accrual 1/9/14

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as quality of life assessment.

Breast Cancer Treatment Outcome Scale (BCTOS) - a 22-item measure of perceived aesthetic (e.g., breast shape) and functional status (e.g., pain, mobility) after breast-conserving surgical treatment (BCT) and radiotherapy.

This brief self-report instrument has high reliability and validity, and it has been used in a variety of previous studies on recovery from breast cancer treatment. These endpoints will be assessed at baseline prior to start of RT, end of radiation, 1 month and 6 months after radiation, and 1, 2 and 3 years after completion of radiation. This tool was also used and at these same time points to facilitate comparisons with the outcomes from RTOG 0413/NSABP B39. This tool includes items that focus specifically on radiotherapy-relevant symptoms (e.g., reports of skin problems, tenderness in the breast, hardness in the breast due to enhanced fibrosis, and pain).

Physician reported cosmetic outcome has been consistently reported from prospective studies evaluating new methods for breast radiation. It is important to demonstrate that physician reported cosmetic outcomes are non-inferior with this novel method as well. Physician assessed cosmetic outcome will be assessed at baseline prior to start of RT but after surgery, 1 year and 3 years using a 4 point scale (Harvard/ EORTC). This scale has been used in prior RTOG studies assessing PBI, and is currently used on the ongoing Phase III study (NSABP B-39/RTOG 0413) comparing standard fractionated WBI to PBI.

11.2.1 Finally, digital images (photographs) will be taken of the treated and untreated breasts, again using RTOG-established protocol. For practical reasons, these digital images will only be taken at three points in time, at baseline (prior to the start of radiation but after surgery) and at the 1-year and 3-year (final) assessment points. Two digital images will be taken at each of these assessment points. One will be a close up of the treated breast alone, in order to provide detailed information regarding the treatment effects. The second digital image will be a straight frontal view of both breasts taken in either a standing or seated position with the patient's hands symmetrically placed on her hips, taking care to exclude her face and framing and focusing on both the treated and untreated breast to allow optimal comparison of the breasts for symmetry.

These photographs will then be uploaded as

J-peg files @ https://silver1.phila.acr.org/clinical_rtog/pgsitetools.html.
(See Appendix VII)

These digital images will later be evaluated for cosmetic results by a panel of physicians using diagnostic criteria established in previous RTOG trials (e.g., degree of scarring, extent of pock marks and/or dimpling, degree of symmetry between the breasts, extent of changes to the skin). We think it is of interest and important to obtain multiple measures of cosmetic outcome, in order to assess the degree of correspondence between physician-generated and patient-generated outcomes. Prior research, taken together with data generated from previous NSABP trials, suggests that physician-generated ratings often underestimate the degree of dissatisfaction experienced and problems perceived by the patient. Our plan is to use the patient's self-report as our primary cosmetic endpoint.

11.3 Measurement of Response

Not applicable to this study

11.4 Criteria for Discontinuation of Protocol Treatment

11.4.1 Progression of disease

11.4.2 A delay in protocol treatment, as specified in Section 6.0

If study therapy is stopped but she still allows the study doctor to follow her care, she should continue to be followed according to the study schedule. Follow up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION

Data should be submitted to:

NRG Oncology*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (1/9/14)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)**	Within 2 weeks of study entry
Slides/Blocks **(P2)**	See Section 10.0
Surgical Pathology Report (**S5**) Surgical Operative report (**S2)**	Within 2 weeks of study entry. Also at time of progression/relapse if applicable.
Digital Images(Photographs) Photograph Submission Notification Form(**T7)** (for patients registered prior to 1/9/14)	Baseline prior to RT but after surgery);1 and 3 years post RT completion

Cosmesis Questionnaires: Patient Reported Cosmesis Questionnaire (**BQ**) (*for patients registered prior to 1/9/14*)	Baseline prior to RT but after surgery);at the completion of RT; 1 and 6 months post RT completion; 1, 2 and 3 years post RT completion
Physician Reported Cosmesis Questionnaire (**QP**) (*for patients registered prior to 1/9/14*)	Baseline (prior to RT start but after surgery);1 and 3 years post RT completion
Follow-up Form **(F1)**	At 1 and 6 months post RT; at 1 year post RT, then annually. Also at progression /relapse and death
Comorbidities & Other Conditions Form **(CF)**	Baseline (prior to study entry); at 6 months post RT completion; at 1 year post RT completion ,then annually

12.2 Summary of Dosimetry Digital Data Submission (10/21/13)

(Submit to TRIAD; see Section 5.2 for account access and installation instructions.)

Item	**Due**
Preliminary Dosimetry Information (DD)	
Digital Data Submission – Treatment Plan submitted to TRIAD by Physicist	Within 1 week of start of RT
Digital data submission includes the following:	
• CT data, critical normal structures, all GTV, CTV, and PTV contours	
• Digital beam geometry for initial and boost beam sets	
• Doses for initial and boost sets of concurrently treated beams	
• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan • All required structures **MUST** be labeled per the table in Section 6.5. • *The "RTOG 1005 Datasheet" is available in the Forms section of the of the NRG Oncology/RTOG web* site, http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1005. Submit via TRIAD with the digital data listed above.	
Upon submission of the digital data via TRIAD, complete an online digital data transmission form (DT) located in the Forms section on the NRG Oncology/RTOG web site at	

http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1005	
Note: All simulation and portal films and/or digital film images will be kept by the institution and only submitted if requested.	
Final Dosimetry Information	Within 1 week of RT end
Radiotherapy Form **(T1) [copy to HQ]** Daily Treatment Record **(T5) [copy to HQ]** Modified digital patient data as required through consultation with Image-Guided Therapy QA Center	

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint

Local failure (failure: the first occurrence of a local-in breast failure)

13.1.2 Secondary Endpoints

- Overall survival (failure: death due to any cause);
- Disease-free survival (failure: local-regional disease recurrence or distant metastases or second primary or death due to any cause);
- Distant disease-free survival (failure: distant metastases or second primary or death due to any cause);
- Adverse events related to treatment;
- Changes in breast-related symptoms and side effects and cosmesis;
- Correlation between dose-volume data and both adverse events and efficacy;
- Translational research of single nucleotide polymorphisms (SNPs) in TGFB1 and ATM genes.
- Treatment costs

13.2 Study Design (16-DEC-2021)

13.2.1 Stratification Variables

Patients will be stratified before randomization with respect to age (< 50 vs. ≥ 50), chemotherapy use (no vs. yes),histologic grade (1, 2 vs. 3)and ER status (+ vs. –). The treatment allocation scheme described by Zelen (1974) will be used because it balances patient factors other than institution.

13.2.2 Sample Size Derivation

The sample size calculations are based on the primary hypothesis that the local failure rate in the hypofractionated arm (Arm 2) will not be significantly worse than in the standard treatment arm (Arm 1). The null hypothesis (H_0) of this test is that the hazard rate of Arm 2 (λ_2) is significantly worse than the hazard rate of Arm 1 (λ_1). The alternative hypothesis (H_A) is that the hazard rate of Arm 2 is not significantly worse than the hazard rate of Arm 1.

$$H_0: \delta \geq \delta_0 \quad \text{vs.} \quad H_A: \delta < \delta_0$$

where $\delta = -\ln(\lambda_2/\lambda_1)$ and δ_0 is a non-inferiority margin.

The estimated rate of local recurrence at 5 years for the control arm of whole breast radiation with sequential boost for this trial is 6%. The justification based upon prospective trials is shown in Table 2 (in Section 1.7.4). Table 3 below shows the estimates for patient enrollment of high-risk subgroups. It is expected the percentage of high risk features to be significantly higher in this trial than previous hypofractionation

trials from Canada (Whelan 2002) and the United Kingdom (START) because these groups are specifically targeted by this study's eligibility. The following patient enrollment is assumed: 65% N0, and 35% N1. The enrollment of node positive patients in the UK START A trial was 29% and START B trial 23%. It is assumed that approximately 50% of patients will be ≤ 50 years of age. In the UK START A 23% were age ≤ 50 and UK START B 21% age ≤ 50 years. In the Whelan study, 25% were ≤ 50 years of age. Because this protocol specifically is limiting eligibility to high risk patients, and excludes low-risk patients > 50 years, node negative patients will be disproportionately younger in order to be eligible, while node positive patients will be expected to have a more typical age distribution. It is assumed that 45% of patients will be grade 3.

The enrollment of grade 3 patients on the UK START A was 28% and START B 23%, and 19% in the trial by Whelan et al. The percentage enrollment on the UK START trials of age < 50, grade 3 or node positive was 56% for trial A and 48% for trial B. It is also assumed that 60% of patients will be ER-positive, and 40% ER-negative. In the Whelan study, the enrollment of ER-negative patients was 27%.

Table 3: Patient Enrollment Estimates

Cohort	Protocol enrollment
N0	65%
N1	35%
Age ≤ 50	50%
Age > 50	50%
Grade 3	45%
ER negative	40%
Neoadjuvant chemo	5%

The protocol will specifically exclude the following patients which have a very low risk of 5-year local recurrence:

1) DCIS and age ≥ 50 years.
2) DCIS and age < 50 years and grade 1 or 2
3) Invasive breast cancer and ≥ 70 years old, T1, N0, ER/PR positive
4) Invasive breast cancer and ≥ 50 years old, T1, N0, Grade 1-2, ER/PR positive.

Based on a control arm 5-year local failure rate of 6%, Table 4 below shows the non-inferiority margin and corresponding sample sizes for 5-year local failure rates for the hypofractionated arm of 9 and 9.5%.

Table 4: Sample Size Calculations

5-Year Control Arm Local Failure Rate	**5-Year Experimental Arm Local Failure Rate**	**Hazard Ratio (Hypo/Control)**	**Non-Inferiority Margin**	**Required Sample Size Evaluable (Total)**
6%	9%	1.52	0.42	2150 (2312)

6%	9.5%	1.61	0.48	1900 (2044)

The required sample size for the primary endpoint of local failure is based on the following conditions:

- Local- failure times are exponentially distributed with (at least approximately) constant hazards in both treatment arms
- The control (standard) arm will have a 5-year local failure rate of 6% (yearly crude hazard of 0.01238)
- The experimental arm will have a 5-year local failure rate of no more than 9% (yearly crude hazard of 0.01886)
- δ_0 = 0.42 (non-inferiority margin)
- Upper limit on hazard ratio (experiment/control) = 1.52
- One-sided test at α = 0.025
- Statistical power of 90% to conclude non-inferiority if HR = 1
- 4 years of accrual with 5 years of follow-up
- Two interim significance tests and a final test are planned

With 90% statistical power to conclude non-inferiority if the HR = 1, a one-sided significance level of 0.025 and the parameters above, 2150 patients will be accrued uniformly over 4 years to reach the required 245 local failure events. Guarding against an ineligibility or lack-of-data rate of up to 7%, the final targeted accrual for this study will be 2312 patients.

Given the impact of treatment crossovers on non-inferiority trials, the rate of treatment crossovers will be closely monitored. Table 5 shows the impact for 5% and 10% crossover rates. If the crossover rate falls between 5% and 10%, the RTOG will discuss with NCI the potential of amending the trial in order to adjust for this crossover so as to maintain the original study parameters. If the crossover rate reaches or exceeds 10%, RTOG will discuss with NCI the feasibility of continuing the trial.

Table 5: Impact of Crossover

Crossover Rate	Adjusted 5-yr Control Rate	Adjusted 5-yr Hypo Rate	Type I Error (0.025 by Design)	Increase in Accrual Time to Maintain Original Parameters
5%	0.0615	0.0885	0.05	0.82 years
10%	0.0631	0.0870	0.08	2.16 years

Redesign (2021)

The redesign was done in accordance with the NCI Policy for Major Design Amendments for Ongoing Randomized Clinical Trials and redesign specifics performed by a statistician independent from the trial.

The statistical design and analysis plan is revised based on the following changes to the assumptions made in the original design, using the completed accrual. These adjustments will allow for timely reporting of the trial results, while maintaining statistical integrity and reflecting current knowledge of the observed local failure rate in the control arm.

1) Change the upper limit on the hazard ratio and the corresponding non-inferiority margin

Based on the currently observed local failure rate in the control arm (Arm 1), the redesign is based on a 5-year local failure rate of 1.59% (yearly hazard =

0.0032). Since this is much lower than the original estimate of 6%, the redesign for the non-inferiority primary endpoint hypothesis will use a larger hazard ratio (HR) upper limit of 2.12 (yearly hazard = 0.0068, corresponding to a non-inferiority margin = 0.75), while maintaining a smaller absolute difference in 5-year local failure rates. The 5-year event rate for the experimental arm (Arm 2) under the null hypothesis of inferiority would be no more than 3.33%, an absolute increase of 1.74% from the control arm, compared to the original design of no more than 9%, which was an absolute increase of 3%.

2) Change the power and significance level to 80% and 0.05, respectively.

The original sample size calculations were based on statistical power of 90% to conclude non-inferiority if HR=1 and a one-sided significance level of 0.025. The redesign is revising these to 80% and 0.05, respectively, to allow for more timely reporting so that the trial may maintain clinical relevancy.

3) Omit the originally planned interim analyses.

Summary:

Assuming a 5-year local failure rate of 1.59% in Arm 1, an upper bound HR of 2.12 for the non-inferiority alternative hypothesis and using a 1-sided significance level of 0.05, an analyzable sample size of at least 2150 patients will provide >80% power to conclude non-inferiority if the HR is 1 when at least 46 IBR events are observed.

If the alternative hypothesis of noninferiority is accepted based on the proposed analyses, a test of superiority also will be conducted to determine if the hypofractionated treatment (Arm 2) is superior to the standard treatment (Arm 1). With 2150 analyzable patients and a one-sided type I error of 0.05, there will be 71% power to detect a reduction in the 5-year local failure rate from 1.59% to 0.8% based on an intention to treat analysis.

13.3 Accrual

Patient accrual is projected to be 45 cases per month, with a ramp-up period in the first 6 months. The expected monthly accrual in months 1 through 3 and months 4 through 6 following the study being broadcast to RTOG membership and placed on the CTSU menu are 0 and 20, respectively. If the total accrual during months 13 through 18 of the study is ≤ 20% of the targeted accrual (< 55 cases in total), then the protocol will be discontinued per NCI-CTEP accrual guidelines for phase III studies. If the total accrual during months 13 through 18 is between 21% and 49% (55 to 133 cases), then the protocol will continue to accrue subjects and will be evaluated again at the end of month 24. If the accrual during months 22 through 24 is at least 50% of the targeted accrual (≥ 68 cases in total), the NCI-CTEP accrual guidelines for phase III studies will have been met and the study will continue accrual; otherwise, the study will be discontinued.

13.4 Analysis Plan (16-DEC-2021)

13.4.1 Statistical Methods

Local failure time will be measured from the date of randomization to the date of first local failure or last follow-up.

The primary hypothesis will be tested using the logrank test comparing the crude (i.e. cause-specific) hazard of local failure between treatment groups. The Cox proportional hazards regression model will be used to estimate the treatment hazard ratio and investigate additional factors that may be related to local failure.

The cumulative probability of local failure in the presence of competing failure events will be estimated by the cumulative incidence method. (Kalbfleish 1980) The cumulative incidence distributions between the two arms will be compared using Gray's test (1988). We note that because competing failure types are not expected to differ between treatment arms, it is anticipated that results from comparing cause-specific hazards or cumulative incidence functions should yield similar inferential results.

Overall survival, disease-free survival, and distant disease-free survival will be estimated by the Kaplan-Meier method (Kaplan 1958) and distributions between the two arms will be compared using the log-rank test (Mantel 1966).

13.4.2 Interim Analysis to Monitor the Study Progress

Interim reports with statistical analyses will be prepared twice per year until the initial treatment results have been presented/published. In general, the interim reports will contain the following information:

- patient accrual rate with a projected completion date (while the study is still accruing)
- total patients accrued
- distributions of important pretreatment and prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm
- compliance rates of treatment delivery

The interim reports will not contain the results from the treatment comparisons with respect to the primary endpoint, overall survival, or any secondary endpoints, with the exception of reporting of adverse events.

Additionally, the rate of treatment crossovers will be evaluated on a quarterly basis, until the last patient has completed treatment. If this rate exceeds 10%, the study will be evaluated for a potential sample size increase to adjust for the crossover effect.

13.4.3 CDUS Reports

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.4.4 Data Monitoring Committee (DMC) Review

To monitor the safety and efficacy of this study, it will be officially reviewed by the NRG Oncology DMC twice a year in conjunction with the NRG Oncology semi-annual meeting and in between meetings as needed.

13.4.5 Significance Testing for Early Termination and/or Reporting

Primary Endpoint: Local Failure

Two interim analyses will be performed when 33% and 67% of the local failure events have occurred, corresponding to 81 and 165 local failure events. At each look, if the experimental arm is significantly better than the standard arm (at $p<0.001$) then accrual will be stopped (if applicable) and the trial results will be reported with the conclusion that the hypo-fractionated WBI arm is non-inferior to the standard fractionated WBI arm with respect to local failure. For the study, a hazard ratio up to 1.52 (hypo/standard) will still result in a conclusion of non-inferiority. At the interim looks, if the lower bound of the 95% confidence interval for the hazard ratio (hypo/standard) is greater than 1.52, then accrual will be stopped (if applicable) and the trial results will be reported, with the conclusion that the hypo-fractionated WBI arm is inferior to the standard fractionated WBI arm with respect to local failure.

In addition to accrual, distributions of pretreatment characteristics, frequency and severity of adverse events, and compliance with protocol treatment, at the first RTOG DMC meeting following the required number of deaths for each planned interim analysis, blinded efficacy results will be reported to the NRG Oncology DMC.

Analysis for Reporting the Initial Treatment Results

The primary hypothesis of this study is that the local failure rate in the hypofractionated arm (Arm 2) will not be significantly worse than in the standard treatment arm (Arm 1). This major analysis will occur after at least 46 local failures have been observed. It will include:

- tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion given
- distributions of important prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm
- compliance rate of treatment delivery
- observed results with respect to the primary and secondary endpoints

All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis. The primary hypothesis of non-inferiority will be tested using the logrank test statistic, comparing the cause-specific hazards, with a 1-sided significance level of 0.05. Additional analyses of treatment effect will be performed using the Cox proportional hazard model with the stratification factors included as fixed covariates, as well as any factors that show an imbalance between the arms. Where feasible, treatment comparisons with respect to the primary endpoint (local failure) will be compared within ethnic and racial categories.

13.5 Quality of Life

13.5.1 Design

The primary endpoint for the breast-related symptoms and side effects of the trial is self-reported cosmesis, using the BCTOS cosmesis scale (Stanton 2001). Patients that do and do not receive chemotherapy will be recruited and analyzed separately to address this cosmesis endpoint. The BCTOS will be collected at baseline, after informed consent has been obtained, end of radiation, 1 month and 6 months after radiation, and 1, 2 and 3 years after completion of radiation; with the primary endpoint focusing on mean change from baseline to 3 years. The goal is to establish that self – reported cosmesis results for the experimental arm are non-inferior to those of the control arm.

Two-hundred and sixty-six evaluable patients provide 90% power, with a one-sided alpha of 0.025, to test the null hypothesis that the mean change in cosmesis score in the experimental arm will be at least 0.4 standard deviations worse than in the control arm. To answer this hypothesis separately in patients that do and do not receive chemotherapy and to allow for up to a 10% attrition rate for the 3-year assessment, 296 patients receiving chemotherapy and 296 patients not receiving chemotherapy will be recruited for the QoL substudy, for a total of 592 patients.

Physician reported cosmesis will also be evaluated at baseline, and 1 & 3 years after completion of radiation, as well as photos being collected at the same time points.

13.5.2 Analysis

The t-test will be used for the primary QoL comparison of mean change in cosmesis score (baseline to 3 years), measured by BCTOS between the treatment arms. In addition to cosmesis, the pain and functional status subscales from the BCTOS will be compared, focusing on change from baseline to 1 year from the completion of radiation. The t-test will also be used to compare the treatment arms for these subscales. Within each of the chemotherapy and non-chemotherapy groups, 266 patients will provide 90% and 85% power to detect effect sizes of 0.4 and 0.37 respectively, with 1-sided alpha levels of 0.025, for these subscales.

Secondary longitudinal analyses, using all of the time points collected, will be evaluated for the three subscales of the BCTOS.

Using photographs collected at baseline, and 1 and 3 years after completion of radiation,
cosmesis will be evaluated by an independent panel using the same scoring scale as reported by the physicians; and will be reported separately for chemotherapy and non-chemotherapy patients.

13.5.3 Missing Quality of Life Data

Processes such as e-mail alerts will be in place to prospectively remind sites about upcoming QoL assessments in order to help minimize the amount of missing data.
The distributions of quality of life data collection patterns over all collection points in each treatment arm will be described. To inspect the missing data mechanism at least a graphical method will be used. A missing completely at random (MCAR) mechanism exists when missing values are randomly distributed across all observations. A missing at random (MAR) mechanism exists when values are not randomly distributed across all observations, rather than one or more sub-samples.

If the cause of missing data is MCAR, list wise deletion (complete case analysis) will be done. If the MAR assumption is supported by the data, then an imputation method such as multiple imputation will be applied to impute missing data.

If the MAR assumption is not supported by the data, then adjusting for covariates (such as the baseline quality of life score) might reduce the conditional association between outcomes and missing values. If missing data patterns look similar when stratified by such covariate(s), then an analysis that adjusts for such covariate(s) will be conducted and an imputation method such as multiple imputation will be applied. If approximate conditional independence cannot be obtained with any set of covariates, then MNAR (missing not at random) must be addressed by an explicit model for the missing data mechanism (Donaldson 2005) and then an imputation method such as multiple imputation will be applied. All results from the imputed analysis using the multiple imputation will be compared to the complete case analysis results to assess any potential biases.

13.6 Treatment Costs

The shorter duration of accelerated WBI with concurrent boost can be expected to lead to lower costs for those procedures based on the time of a patient's treatment compared to standard WBI with sequential boost, but the type and intensity of procedures may differ between the two study arms. For example the distribution of treatment approaches, e.g. IMRT, 3DCRT, may differ between the study arms. Patients treated with hypofractionated WBI with concomitant boost may be more likely to receive IMRT than patients treated with standard WBI with sequential boost and the difference in approach could lead to higher treatment costs. A cost model will be developed for each study arm with each of the possible treatment approaches, and the procedures used in each approach. The model will use the actual distribution of type of treatment approach in each study arm and Medicare relative value units and conversion factors to estimate and compare treatment costs for each study arm and each type of treatment. The model will also include stratification and patient risk factors. The primary cost analysis will test whether hypofractionated WBI with concurrent boost is not higher in treatment cost than standard WBI with sequential boost.

13.7 Gender and Minorities

Women of all races and ethnic groups are eligible for this study. In conformance with the national Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, possible interactions between race/ethnicity and treatment have been considered. Based on NSABP B-39/RTOG 0413, it is projected that 3% of the patients will be of Hispanic or Latino ethnicity and 97% will not; racial distribution are projected to be 91% white, 6% black or African American, 2.5% Asian and < 1% for both American Indian or Native Alaskan and Native Hawaiian or other pacific

islander. The projected non-White and Hispanic/Latino accrual rates are too low for any meaningful treatment comparisons.

The following table lists the projected accrual by gender, ethnic, and racial categories.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	58	N/A	58
Not Hispanic or Latino	2254	N/A	2254
Ethnic Category: Total of all subjects	2312	N/A	**2312**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	2	N/A	2
Asian	58	N/A	58
Black or African American	139	N/A	139
Native Hawaiian or other Pacific Islander	9	N/A	9
White	2104	N/A	2104
Racial Category: Total of all subjects	2312	N/A	**2312**

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APPENDIX I (5/6/13)
STUDY PARAMETER TABLES

Pre-Treatment Assessments

Assessments	Within 180 days prior to study entry*	Within 90 days of diagnostic, biopsy of the affected breast establishing diagnosis	Within 50 days from study entry	Within 28 days prior to study entry	Within 14 days prior to study entry
Last surgery (breast/axilla)/ last chemo			X		
History and Physical, Zubrod and weight documentation				X	
Breast Examination*				X	
Right and Left Mammogram		X			
CT scan of ipsilateral breast for treatment planning				X*	
Performance status				X	
CBC w/ diff & ANC					X
Chemistry panel					X
Determination of hormone receptor status	Prior to study entry. See section 3.1.11				
Serum or urine pregnancy test (if applicable)					X
Bone scan	X*				
CT of chest, ab, and pelvis or PET/CT	X*				
Negative post-excision mammogram	Recommended*				

*See sections 4.0 and 11.1 for exceptions and details

Assessments During Treatment (1/9/14)

Assessments	**Prior to Start of RT**	**Weekly During RT**	**Last Day of RT**
History and Physical, Zubrod and weight documentation		X	X
Breast Assessment *		X	X
Performance status		X	X
Adverse event evaluation		X	X
Specimens for research-(if patient consents)	X		
Cosmesis/QOLStudy (if patient consents) (for patients registered prior to 1/9/14) ***NOTE**: Non-chemotherapy Cosmesis subset closed to accrual 3/8/13;chemotherapy Cosmesis subset closed to accrual 1/9/14* ▪ Doctor cosmetic assessment (questionnaire and photos)	X		
▪ Patient questionnaire (BCTOS)	X		X

*See section 11.1 for details

Follow-Up Assessments

Assessments	**1 Month After RT Completion**	**6 Months After RT Completion**	**1 Year After RT Completion Then Annually**
History and Physical, Zubrod and weight documentation	X	X	X
Breast Examination *	X	X	X
Bilateral or Right and Left Mammography			X
Ipsilateral Mammography of the treated breast		X	
Performance status	X	X	X
Adverse event evaluation	X	X	X
Cosmesis/QOLStudy (if patient consents) (for patients registered prior to 1/9/14) ***NOTE**: Non-chemotherapy Cosmesis subset closed to accrual 3/8/13;chemotherapy Cosmesis subset closed to accrual 1/9/14* ▪ Doctor cosmetic assessment (questionnaire and photos)			X (and @ year 3
▪ Patient questionnaire (BCTOS)	X	X	X (for 3 yrs)

*See section 11.1 for details

APPENDIX II

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
2	**Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed**
5	**Death**

APPENDIX III

AJCC STAGING SYSTEM

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

Breast

Primary Tumor (T)

The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cutoff for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2.0 cm. Designation should be made with the subscript "c" or "p" modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor.
Tis	Carcinoma *in situ*
Tis (DCIS)	Ductal carcinoma *in situ*
Tis (LCIS)	Lobular carcinoma *in situ*
Tis (Paget's)	Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules). *Note*: Invasion of the dermis alone does not qualify as T4
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including *peau d'orange*) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma (see "Rules for Classification") *Note*: Inflammatory carcinoma is restricted to cases with typical skin changes involving a third or more of the skin of the breast. While the histologic presence of invasive carcinoma invading dermal lymphatics is supportive of the diagnosis, it is not required, nor is dermal lymphatic invasion without typical clinical findings sufficient for a diagnosis of inflammatory breast cancer.

Regional Lymph Nodes (N) *Clinical*

NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the *absence* of clinically evident

axillary lymph node metastases

N2a Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures

N2b Metastases only in clinically detected* ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases

N3 Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

N3a Metastases in ipsilateral infraclavicular lymph node(s)

N3b Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)

N3c Metastases in ipsilateral supraclavicular lymph node(s)

**Note: Clinically detected* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically
detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status
will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.

Regional Lymph Nodes *Pathologic (pN)**

pNX Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)

pN0 No regional lymph node metastasis identified histologically

**Note*: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded
from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.

pN0(i-) No regional lymph node metastases histologically, negative IHC

pN0(i+) Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)

pN0 (mol-) No regional lymph node metastases histologically, negative molecular findings (RT-PCR)

pN0 (mol+) Positive molecular findings (RT-PCR),** but no regional lymph node metastases detected by histology or IHC

pN1 Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***

pN1mi Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)

pN1a Metastases in 1-3 axillary lymph nodes, at least one metastasis greater than 2.0 mm

pN1b Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***

pN1c Metastases in 1-3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected

pN2 Metastases in 4-9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases

pN2a Metastases in 4-9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)

pN2b Metastases in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases

pN3 Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***; or in ipsilateral supraclavicular lymph nodes

pN3a Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes

pN3b Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***

pN3c Metastases in ipsilateral supraclavicular lymph nodes

**Notes*:

*Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn).

**RT-PCR: reverse transcriptase/polymerase chain reaction

***"Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

****"Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

Distant Metastasis (M)

M0 No clinical or radiographic evidence of distant metastases

cM0(i+) No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases

M1 Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0

Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

**Notes*:

*T1 includes T1mi.

**T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

M0 includes M0(i+).

- The designation pM0 is not valid; any M0 should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
- Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.
- Post neoadjuvant therapy is designated with “yc” or “yp” prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, y

APPENDIX IV (10/21/13)

Appendices for NRG Oncology Biospecimen Collection

NRG Oncology FFPE Specimen Plug Kit Instructions

NRG Oncology Blood Collection Kit Instructions

Shipping Instructions:

US Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
UCSF Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For ALL Frozen or Trackable Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

- ❑ Include all **NRG Oncology** paperwork in pocket of biohazard bag.
- ❑ Check that the ST has the consent boxes checked off.
- ❑ Check that all samples are labeled with NRG Oncology study and case number, and include date of collection as well as collection time point.

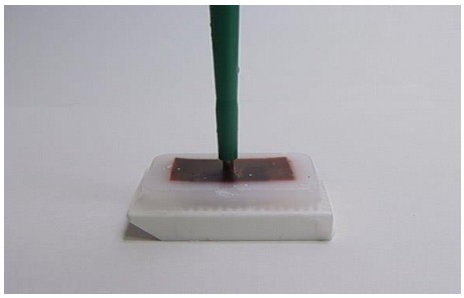
- ❑ **FFPE Specimens:**
  - o Slides should be shipped in a plastic slide holder/ slide box. Place a small wad of padding in top of container If you can hear the slides shaking they are likely to break during shipping.
  - o FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear them shaking they might break during shipping.
  - o Slides, Blocks or Plugs can be shipped ambient or with a cold pack either by USPS to the USPS address (94143) or by Courier to the Street Address (94115). Do NOT ship on Dry Ice.

- ❑ **Frozen Specimens**:
  - o Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified. If possible keep serum, plasma, and whole blood submissions in separate bags.
  - o Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - o Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - o Send frozen specimens on dry ice via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80C until ready to ship.

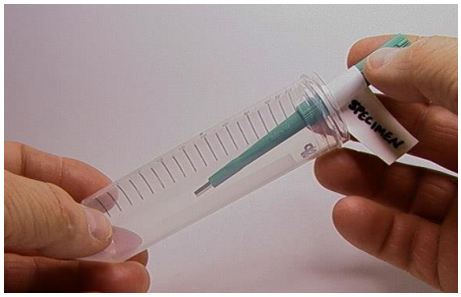
- ❑ **For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bank by email at: RTOG@ucsf.edu or (415)-476-7864 or fax (415)-476-5271.**

NRG Oncology FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank. The plug kit contains a shipping tube and a punch tool.

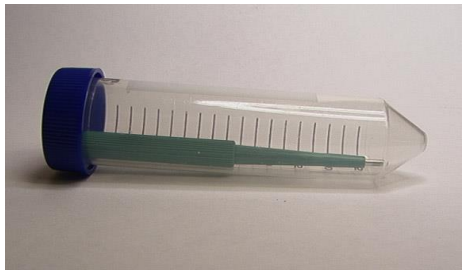


Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.



Step 2
Label the punch tool with the proper specimen ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.



Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

***NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Bank and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below:
For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the NRG Oncology Biospecimen Bank by email at: RTOG@ucsf.edu or call 415-476-7864 /FAX 476-5271;

U.S. Postal Service Mailing Address: <u>For Non-frozen Specimens Only</u>
NRG Oncology Biospecimen Bank
University of California San Francisco
UCSF Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): <u>For ALL Frozen Specimens or Trackable shipments</u>
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

NRG Oncology BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of plasma and whole blood ***(as specified by the protocol)***:

Kit contents:

- One Purple Top EDTA tube for plasma (A)
- One Purple Top EDTA tube for Whole Blood (B)
- Twenty (20) 1 ml cryovials
- Absorbent shipping material (3)
- Biohazard bags (3)
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Kit Instructions
- Specimen Transmittal Form
- UN1845 DRY Ice Sticker
- UN3373 Biological Substance Category B Stickers

Preparation and Processing of Plasma and Whole Blood:

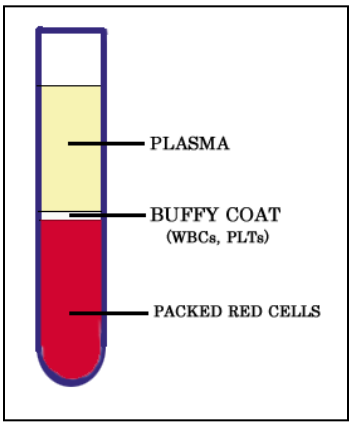
PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection time point on ST.

A) Plasma): Purple Top EDTA tube #1

- ❑ Label as many 1ml cryovials (5 to 10) as necessary for the plasma collected. Label them with the RTOG study and case number, collection date, time and time point, and clearly mark cryovials "plasma".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5 to 10) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma". Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C
6. Store frozen plasma -70 to -90° C until ready to ship on dry ice.
7. See below for storage conditions.



PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection timepoint on ST.

B) Whole Blood For DNA: Purple Top EDTA tube #2

- ❑ Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the NRG Oncology study and case number, collection date/ time, and clearly mark cryovials "blood".

Process:

1. After collection, invert tube(s) multiple multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (3 to 5) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen -70 to -90° C until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection time point on ST.

Storage and Shipping:

Freezing and Storage:

- ☐ Freeze Blood samples in a -80C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20° C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only- Canada Mon-Tues).
  - OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only- Canada Mon-Tues).
  - OR:
  - Samples can be stored in lid. nitrogen vapor phase (ship out Monday-Wednesday only- Canada Mon-Tues).
- ❑ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all NRG Oncology paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ For questions regarding collection, shipping or to order a Blood Collection Kit, please Email RTOG@ucsf.edu or call (415)476-7864.

Shipping Address :

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476- 7864 or e-mail: RTOG@ucsf.edu

APPENDIX V (5/6/13)

RADIATION THERAPY SAMPLE TREATMENT PLANS

CONTOURING GUIDELINES

1 Contouring Targets and Organs at Risk (OAR):

Contouring accurately and consistently is essential for case evaluation and the data comparison necessary to achieve the primary and secondary endpoints of this protocol. The structures to be contoured are the same in both arms 1 and 2.

The targets to be contoured in every case are:

- Lumpectomy
- Lumpectomy clinical target volume (CTV)
- Lumpectomy planning target volume (PTV)
- Lumpectomy planning target volume for evaluation (PTV-eval)
- Breast CTV
- Breast PTV
- Breast PTV-eval

The following OAR will be contoured on all cases:

- Ipsilateral lung
- Contralateral lung
- Heart
- Contralateral breast
- Thyroid.

2 Contouring Targets:

The targets to be contoured are listed in the protocol under section 6.4.2 are listed below with accompanying figures 1- 5.

2.1 Lumpectomy Target Volumes

2.1.1 Lumpectomy: (Figure 1.) For this protocol the term “lumpectomy” will represent the surgical cavity from the breast conserving surgery. This is to replace the typical gross tumor volume designation (GTV) used in other disease sites or when the tumor is insitu. Contour using all available clinical and radiographic information including the excision cavity volume, architectural distortion, lumpectomy scar, seroma and/or extent of surgical clips (clips are strongly recommended). Patients without a clearly identifiable excision cavity are not eligible for protocol participation.

2.1.2 Lumpectomy Clinical Target Volume (CTV): (Figure 1.) The Lumpectomy CTV consists of the contoured Lumpectomy plus a 1 cm 3D expansion with the following 3 limitations: 1. limit the CTV posteriorly at anterior surface of the pectoralis major; 2. limit anterolaterally 5 mm from skin; and 3. should not cross midline. In general, the pectoralis muscles and/or serratus anterior muscles are excluded from the lumpectomy CTV unless clinically warranted by the patient’s pathology.

2.1.3 Lumpectomy Planning Target Volume (PTV): (Figure 2.) The lumpectomy PTV is a 7 mm expansion on the Lumpectomy CTV and excludes the heart. This is the structure used for beam aperture generation.

2.1.4 Lumpectomy Planning Target Volume for evaluation (PTV_EVAL) (Figure 3.). This Lumpectomy PTV_EVAL is limited to exclude the portion of the PTV that extends outside the ipsilateral breast beyond skin or into the chest wall or thorax.

The lumpectomy PTV-eval consists of the lumpectomy PTV excluding the first 5 mm of tissue under the skin (in order to remove most of the buildup region for the DVH analysis) and excluding the Lumpectomy PTV expansion beyond the posterior extent of breast tissue (chest wall, pectoralis muscles and lung) when pertinent. This Lumpectomy PTV_EVAL is the structure used for DVH constraints and analysis.

Figure 1. Lumpectomy and Lumpectomy Clinical Target Volume (CTV)

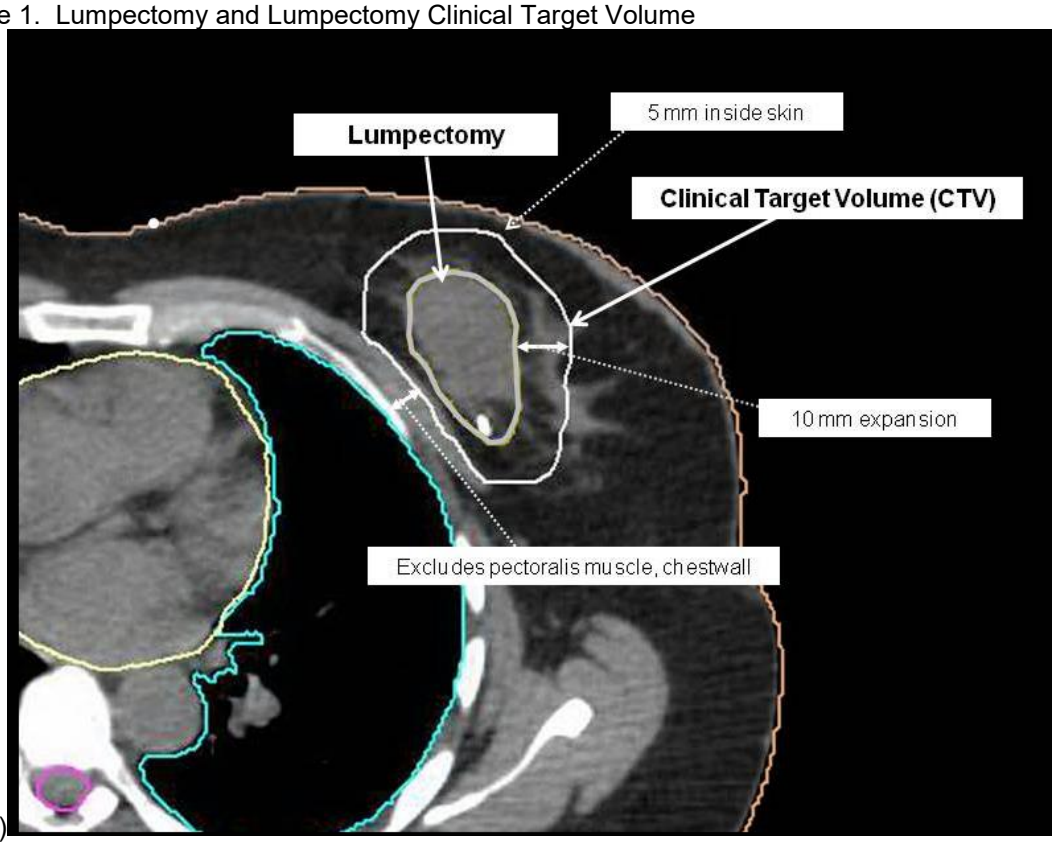


Figure 2. Lumpectomy Planning Target Volume (PTV)

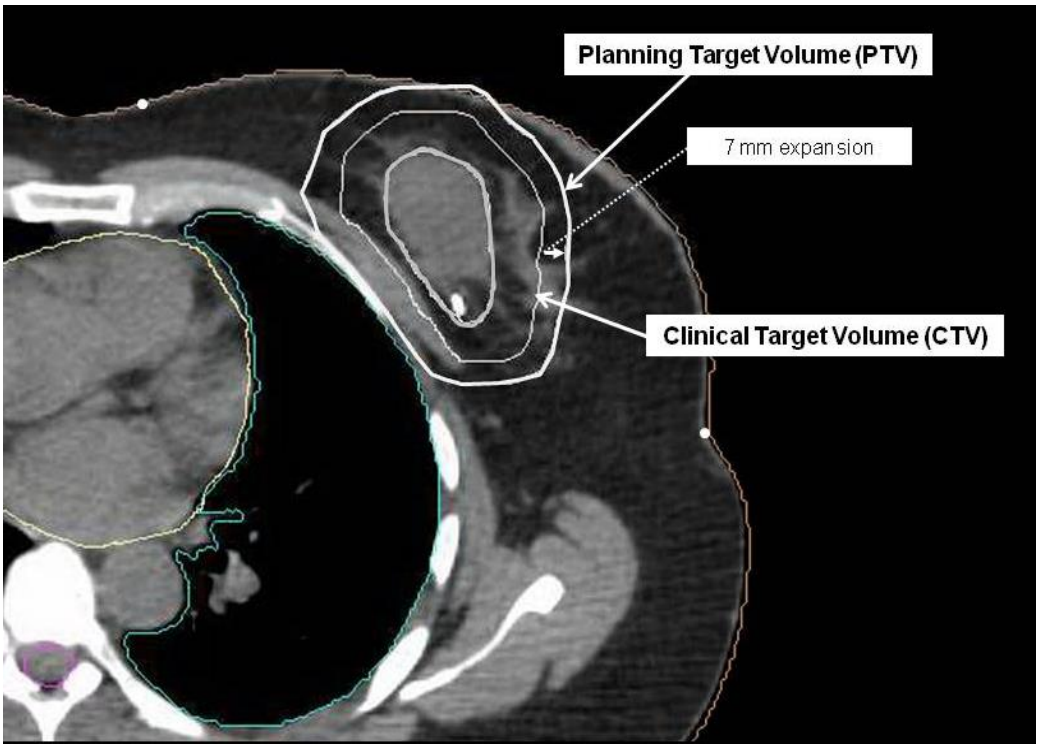
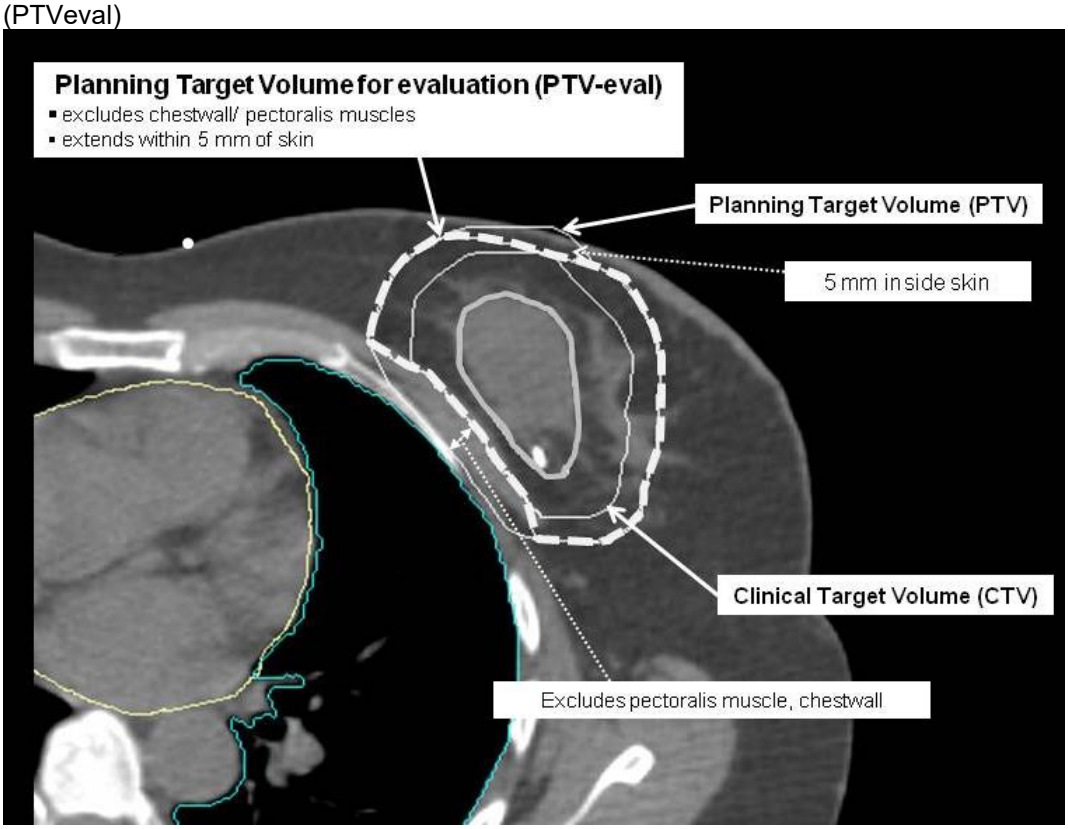


Figure 3. Lumpectomy Planning Target Volume for Evaluation (PTVeval)



2.2 Breast Target Volumes

2.2.1 Breast Clinical Target Volume (CTV): (figure 4.), Consists of and takes into account the clinical borders placed at the time of CT simulation, the apparent glandular and fatty breast tissue visualized by CT, consensus definitions of anatomical borders from the RTOG breast cancer atlas, and should include the Lumpectomy CTV. The breast CTV is limited anteriorly within 5 mm from the skin and posteriorly to the anterior surface of the pectoralis muscles, serratus anterior muscle/ chestwall, boney thorax and lung. In general, the pectoralis and serratous anterior muscles/chestwall are excluded from the breast CTV unless clinically warranted by the patient's pathology. RTOG anatomy consensus guidelines are available at:
(http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx)

2.2.2 Breast Planning Target Volume (PTV): (figure 4.): Consists of the Breast CTV generated above plus a 7 mm 3D expansion (excluding heart and not to cross midline). This is the structure used for beam aperture generation.

2.2.3 Breast Planning Target Evaluation for evaluation (PTV eval): (figure 5) This Breast PTV_EVAL is intended to exclude the portion of the breast PTV that extends outside the outside the patient or into the boney thorax and lungs. This Breast PTV_EVAL consists of the breast PTV limited to exclude the part anteriorly 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 no deeper to the anterior surface of the ribs (excludes boney thorax and lung). This Breast PTV_EVAL is the structure used for DVH constraints and analysis.

Figure 4. Breast Clinical Target Volumes (CTV) and Breast Planning Target Volumes (PTV)

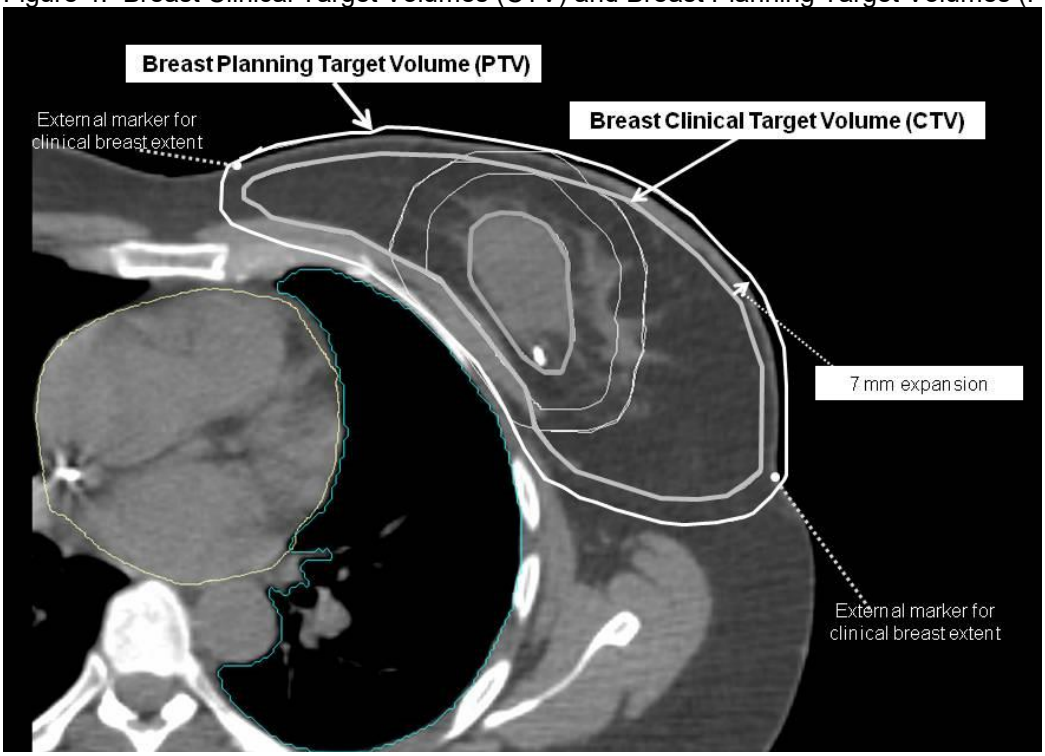
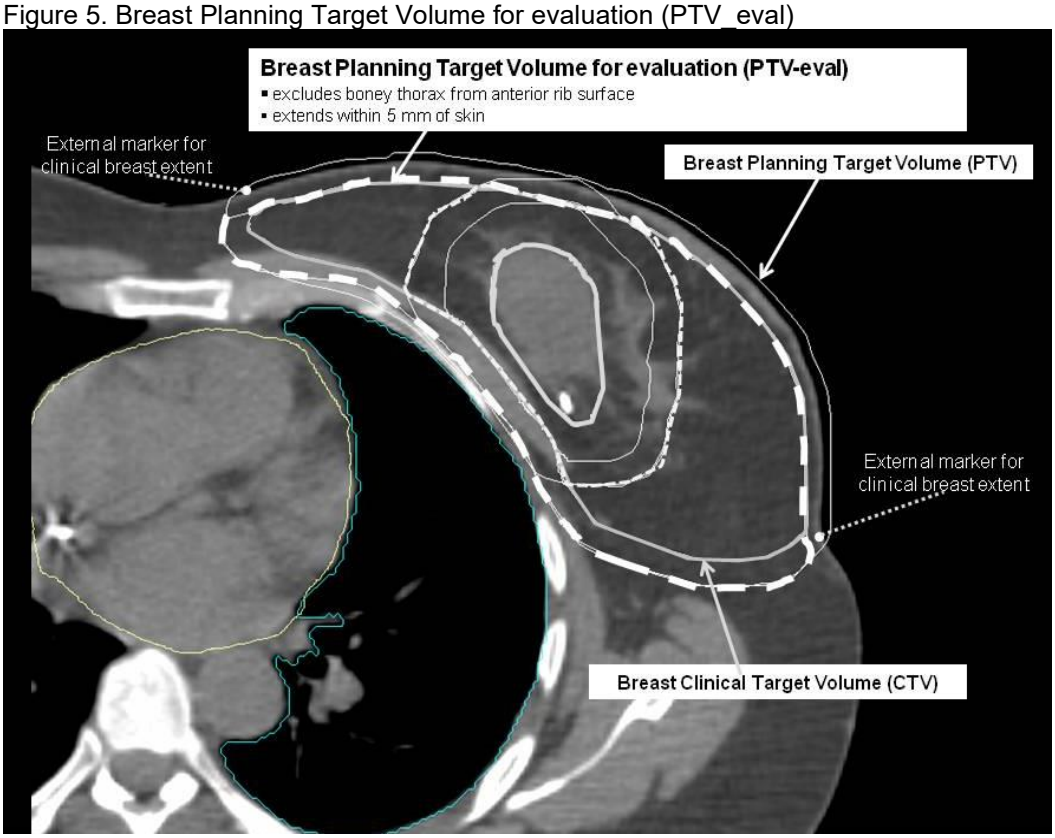


Figure 5. Breast Planning Target Volume for evaluation (PTV_eval)



3 Organs at Risk (OAR)

The OAR to be contoured on all cases are the ipsilateral and contralateral lung, heart, thyroid and contralateral breast.

3.1 Ipsilateral and contralateral Lung: This may be contoured with auto-segmentation with manual verification.

3.2 Heart: *This is to be contoured on all cases- not just the left sided ones*. 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.

3.3 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 fo the thyroid are somewhat triangular in shape and often do not converge anteriorly at mid-line. All "bright" thyroid tissue should be contoured.

3.4 Contralateral Breast: Includes contralateral breast as defined by clinical markers
And the apparent CT glandular breast tissue visualized by CT and consensus definitions of anatomical borders from the RTOG Breast Atlas. In general the borders are:
Posterior border: At the anterior surface of the pectoralis, serratous 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.
Cephald border: Should be similar to that of the ipsilateral breast CTV
Caudal:border: Inframammary fold and 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.
RTOG anatomy consensus guidelines are available at:
(http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx)

APPENDIX VI (5/6/13)

DOSE VOLUME HISTOGRAM CONSTRAINTS

All maximum doses should be defined in one dose calculation voxel, e.g., 3x3x3 mm^3.

The conformity index is an optional constraint, but must be recorded and reported on all cases

Breast PTV Eval

Breast PTV eval Description	Constraint			**ARM I** 50 Gy in 25 sequential 12-14 Gy boost total 62-64 Gy	**ARM I** 42.7 in 16 sequential 12-14 Gy boost total 54.7-56.7 Gy	**ARM II** 40 Gy in 15 concurrent boost to 48 Gy
	Goal	Volume	Dose			
Breast PTV Eval receiving whole-breast dose	Per Protocol	at least 95% of the breast PTV Eval receives	at least 95% of whole breast dose which is	47.5 Gy	40.6 Gy	38 Gy
	Variation Acceptable	at least 90% of the breast PTV Eval receives	at least 90% of whole breast dose which is	45 Gy	38.4 Gy	36 Gy
Breast PTV Eval receiving boost dose	Per Protocol	no more than 30% of the breast PTV Eval	exceeds 100% of boost dose which is	62-64 Gy	54.7-56.7 Gy	48 Gy
	Variation Acceptable	no more than 35% of the breast PTV Eval	exceeds 100% of boost dose which is	62-64 Gy	54.7-56.7 Gy	48 Gy
Breast PTV Eval receiving above the whole-breast dose	Per Protocol	no more than 50% of the breast PTV Eval	exceeds 108% of whole breast dose which is	54 Gy	46.1 Gy	43.2 Gy
	Variation Acceptable	no more than 50% of the of the breast PTV Eval	exceeds 112% of whole breast dose which is	56 Gy	47.8 Gy	44.8 Gy
Breast PTV Eval maximum dose	Per Protocol		does not exceed 115% of prescription whole breast dose which is	57.5 Gy	49.1 Gy	46 Gy
	Variation Acceptable		does not exceed 120% of prescription	60 Gy	51.2 Gy	48 Gy

			whole breast dose which is			
Conformity Index (Ratio of volume covered by 95% prescription isodose / volume of Breast PTV Eval)	Per Protocol		no less than 0.95 and no more than 2.0			
	Variation Acceptable		No less than 0.85 and no more than 2.5			

Lumpectomy PTV Eval

Lumpectomy PTV Eval Description	Constraint			**ARM I** 50 Gy in 25 sequential 12-14 Gy boost total 62-64 Gy	**ARM I** 42.7 in 16 sequential 12-14 Gy boost total 54.7-56.7 Gy	**ARM II** 40 Gy in 15 concurrent boost to 48 Gy
	Goal	Volume	Dose			
Lumpectomy PTV Eval receiving boost dose	Per Protocol	at least 95% of the lumpectomy PTV Eval receives	at least 95% of boost dose which is	58.9-60.8 Gy	52-53.9 Gy	45.6 Gy
	Variation Acceptable	at least 90% of the lumpectomy PTV Eval receives	at least 90% of boost dose which is	55.8-57.6 Gy	49.2-51 Gy	43.2 Gy
Lumpectomy PTV Eval receiving above boost dose	Per Protocol	no more than 5% of the lumpectomy PTV Eval	exceeds 110% of boost dose which is	68.2-70.4 Gy	60.2-62.4 Gy	52.8 Gy
	Variation Acceptable	no more than 10% of the lumpectomy PTV Eval	exceeds 110% of boost dose which is	68.2-70.4 Gy	60.2-62.4 Gy	52.8 Gy
Lumpectomy PTV Eval maximum dose	Per Protocol		does not exceed 115% of boost dose which is	71.3-73.6 Gy	62.9-65.2 Gy	55.2 Gy
	Variation Acceptable		does not exceed 120% of boost dose which is	74.4-76.8 Gy	65.6-68 Gy	57.6 Gy

Conformity Index (Ratio of volume covered by 95% prescription isodose / volume of Lumpectomy PTV Eval)	Per Protocol		No less than 0.95 and no more than 2.5			
	Variation Acceptable		No less than 0.9 and no more than 3			

Normal Tissue Constraints

Description		Volume	ARM I	ARM II
Heart dose constraint 1	Per Protocol	no more than 5% of the heart for left-sided cancer 0% of the heart for right-sided exceeds	20 Gy	16 Gy
	Variation Acceptable	no more than 5% of the heart for left-sided cancer 0% of the heart for right-sided exceeds	25 Gy	20 Gy
Description		Volume	ARM I	ARM II
Heart dose constraint 2	Per Protocol	no more than 30% of the heart for left-sided cancer no more than 10% of the heart for right-sided exceeds	10 Gy	8 Gy
	Variation Acceptable	no more than 35% of the heart for left-sided cancer no more than 15% of the heart for right-sided exceeds	10 Gy	8 Gy
Heart dose constraint 3	Per Protocol	Mean dose does not exceed	400 cGy	320 cGy
	Variation Acceptable	Mean dose does not exceed	500 cGy	400 cGy
Ipsilateral lung dose	Per Protocol	no more than 15% of the ipsilateral lung exceeds	20 Gy	16 Gy
	Variation Acceptable	no more than 20% of the ipsilateral lung exceeds	20 Gy	16 Gy
Ipsilateral lung dose constraint 1	Per Protocol	no more than 35% of the ipsilateral lung exceeds	10 Gy	8 Gy
	Variation Acceptable	no more than 40% of the ipsilateral lung exceeds	10 Gy	8 Gy
Ipsilateral lung dose constraint 2	Per Protocol	no more than 50% of the ipsilateral lung exceeds	5 Gy	4 Gy

	Variation Acceptable	no more than 55% of the ipsilateral lung exceeds	5 Gy	4 Gy
Contralateral Lung	Per Protocol	no more than 10% exceeds	5 Gy	4 Gy
	Variation Acceptable	no more than 15% exceeds	5 Gy	4 Gy
Contralateral Breast	Per Protocol	Dmax does not exceed / no more than 5% exceeds	310 / 186 cGy	240 / 144 cGy
	Variation Acceptable	Dmax does not exceed / no more than 5% exceeds	496 / 310cGy	384 / 240 cGy
Thyroid	Per Protocol	Max point dose does not exceed 2% of prescribed dose which is	1.24-1.28 Gy for 62-64 Gy prescribed dose or 1.09-1.13 Gy for 54.7-56.7 Gy prescribed dose	0.96 Gy
	Variation Acceptable	Max point dose does not exceed 3% of prescribed dose which is	1.86-1.92 Gy for 62-64 Gy prescribed dose or 1.64-1.7 Gy for 54.7-56.7 Gy prescribed dose	1.44 Gy

APPENDIX VII (5/6/13)

INSTRUCTIONS FOR SUBMITTING COSMESIS PHOTOS

To submit cosmesis photos:

- **Make sure photos are available in a JPEG format on the computer that you are using-Identify the photos as follows:**
  Baseline photos-Single_B forTreated Breast view Both_B for Both Breasts view
  1-year photos - Single_1 for Treated Breast view Both_2 for Both Breasts view
  3-yearphotos- Single_3 for Treated breast view Both_3 for Both Breasts view
- **Go to http://www.rtog.org/**
- **Click on site tools link at the top of the page**
- **Click on RTOG Cosmesis Upload Tool**
- **Click on RTOG 1005**
- **Log in using your personal ID and Password**
- **Complete the required fields and upload the photos**
- **Please be sure to upload one photo of the treated breast and one photo showing both breasts as instructed in Section 11.2.1 of the protocol**