NRG-BR007: A PHASE III CLINICAL TRIAL EVALUATING DE-ESCALATION OF BREAST RADIATION FOR CONSERVATIVE TREATMENT OF STAGE I, HORMONE SENSITIVE, HER2-NEGATIVE, ONCOTYPE RECURRENCE SCORE ≤ 18 BREAST CANCER

(DEBRA*)

* DE-escalation of Breast RAdiation (DEBRA)

ClinicalTrials.gov Identifier NCT# TBD
NCI Version Date: (March 5, 2021)

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SWOG / SWOG
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Two Allegheny Center – Suite 1200 |
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<td>Susan McNulty, BS RT (R) (T), CMD</td>
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<th>For regulatory requirements:</th>
<th>For patient enrollments:</th>
<th>For data submission:</th>
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<td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.</td>
<td>Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at <a href="https://www.ctsu.org/OPEN_SYSTEM/">https://www.ctsu.org/OPEN_SYSTEM/</a> or <a href="https://OPEN.ctsu.org">https://OPEN.ctsu.org</a>. Contact the CTSU Help Desk with any OPEN related questions by phone or email: 1-888-823-5923, or <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a>.</td>
<td>Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions. Do not submit study data or forms to the CTSU. Do not copy the CTSU on data submissions.</td>
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<tr>
<td>Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</td>
<td></td>
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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.

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

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For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission)

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Step 1 – Pre-entry registration
If patients with a $T1a$ tumor ($\leq 0.5$ cm in size) do **not** have an Oncotype DX Recurrence Score, a tissue sample must be sent to the Genomic Health centralized laboratory.

**STRATIFICATION**
- Age ($< 60; \geq 60$)
- RS ($\leq 11, > 11$)
- Tumor size ($\leq 1$ cm; $1.1–2$ cm)

**Step 2-RANDOMIZATION**

**Arm 1**
- Breast Radiation Therapy
- Endocrine Therapy

**Arm 2**
- No Breast Radiation Therapy
- Endocrine Therapy

* Randomization is 1:1.
** See Section 5.0 for radiation therapy and endocrine therapy information.
1.0 OBJECTIVES

1.1 Primary Objective

To evaluate whether breast conservation surgery and endocrine therapy results in a non-inferior rate of invasive or non-invasive ipsilateral breast tumor recurrence (IBTR) compared to breast conservation with breast radiation and endocrine therapy.

1.2 Secondary Objectives

1.2.1 To evaluate whether breast conservation surgery and endocrine therapy inclusive of any second breast conservation surgery for salvage of IBTR results in a non-inferior rate of overall breast conservation compared to breast conserving surgery, endocrine therapy and radiation for IBTR.

1.2.2 To evaluate whether breast conservation surgery and endocrine therapy results in a non-inferior rate of invasive ipsilateral breast tumor recurrence (IIBTR) compared to breast conservation, breast radiation, and endocrine therapy.

1.2.3 To evaluate whether breast conservation surgery and endocrine therapy results in a non-inferior relapse free interval (RFI) compared to breast conservation, breast radiation, and endocrine therapy.

1.2.4 To evaluate whether breast conservation surgery and endocrine therapy results in a non-inferior distant disease-free survival (DDFS) compared to breast conservation, breast radiation, and endocrine therapy.

1.2.5 To evaluate whether breast conservation surgery and endocrine therapy results in a non-inferior overall survival (OS) compared to breast conservation, breast radiation, and endocrine therapy.

1.2.6 To evaluate whether there is a difference in patient-reported breast pain in women who do and do not receive breast radiation.

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1.2.8 To evaluate whether adherence to endocrine therapy following breast conservation surgery alone is non inferior compared to endocrine therapy with breast conservation surgery and breast radiation.

2.0 BACKGROUND

2.1 Introduction

Breast conservation therapy for early stage breast cancer has been an important achievement of oncology practice in the last half century and breast radiotherapy (RT) has been essential in its development. Several seminal randomized clinical trials conducted in the 1980’s era demonstrated that breast radiotherapy following lumpectomy yielded overall survival outcomes equivalent to mastectomy for treatment of early stage invasive breast cancer (Blichert-Toft 2008, Fisher 2002, Litiere 2012, Veronesi 2002) leading to the National Institute of Health (NIH) Consensus Conference statement in 1991 supporting breast conservation treatment (NIH Consensus Conference 1991). This established lumpectomy with RT as an alternative to mastectomy and subsequently the rate of breast conservation for eligible breast cancer patients rose steadily. Shortly thereafter, investigators recognized that the toxicity, patient burden, and geographic barriers associated with the protracted treatment course for breast RT was a potential barrier to breast conservation utilization. Numerous phase III clinical trials were conducted...
randomizing women post lumpectomy to RT vs. observation aimed at identifying which cases did not derive a significant RT benefit (Clark 1996, Liljegren 1999, Veronesi 2001, Clarke 2005). No such subsets of breast cancer patients were consistently identified, thereby solidifying the standard that breast conservation required both lumpectomy and RT. Two meta-analyses by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) in 2005 and 2011 further reinforced the value of breast RT post lumpectomy by examining the relationship of local recurrence and breast cancer mortality relative to the use of breast RT post lumpectomy. In each analysis, it found for axillary node negative breast cancer patients undergoing breast conservation a small but consistent increase in breast cancer mortality when breast radiotherapy was omitted (Clarke 2005, EBCTCG 2011). As a result, breast RT after lumpectomy has become an established paradigm for breast conservation for early stage breast cancer and is recommended by the NCCN 2018 guidelines (as it has for nearly two decades) that are commonly used today by clinicians and health systems alike (NCCN 2018).

The landscape of early stage breast cancer has changed dramatically over the past three decades since the establishment of breast conservation. Widespread screening with mammography has led to the diagnosis of smaller and earlier stage disease. All breast cancers are now routinely characterized by their hormone sensitivity based on the presence of estrogen and progesterone receptors on tumor cells within the biopsy or surgical specimen and presence of HER2 (human epidermal growth factor receptor 2) which has provided an additional means of stratifying breast cancer into distinct prognostic groups. Small, node negative invasive breast cancer that is hormone sensitive (HS) and HER2-negative has a lower overall recurrence rate (local, regional, and distant) than breast cancers characterized by more adverse clinical pathologic features. However, other than in a smaller subset of women greater than 70 years old (Hughes 2013), clinical trials in this HS population still demonstrated unacceptable local recurrence risks long term after lumpectomy alone (Fyles 2004, Winzer 2010) emphasizing that clinical and pathologic features are insufficient for consistently identifying when RT can safely be omitted.

2.2 Evidence that Biomarkers can Identify Patients at Sufficiently Low Risk of Recurrence after Lumpectomy that Radiation can be Omitted

Over the past decade, numerous biomarkers have emerged for guiding adjuvant systemic therapy decision making for early stage breast cancer (Harris 2016). The Oncotype DX™ Recurrence Score (RS) is a commercially available multigene assay using RNA expression profiling that has been demonstrated in a large phase III randomize trial to reliably predict the risk of distant metastasis and chemotherapy benefit in node-negative hormone sensitive breast cancer patients receiving endocrine treatment (Sparano 2018). This now allows tens of thousands of women annually to omit chemotherapy and its associated toxicities from their breast cancer treatment. The RS has proven to be prognostic for local regional recurrence (LRR) as well when retrospectively studied in node-negative, ER-positive breast cancer in NSABP B-14 and B-20 clinical trial samples (Mamounas 2010). In this analysis, among 895 tamoxifen-treated patients, 390 underwent lumpectomy and radiation, and the 10-year actuarial rates of LRR for the RS low, intermediate, and high groups were 6.8%, 10.8%, and 14.6%, respectively (P =0.043). For breast conservation cases, RS was an independent predictor of LRR, as well as patient age less than 50 years, in multivariate analysis. Similarly, among 388 women with hormone receptor-positive, node-negative breast cancer treated with chemotherapy plus endocrine therapy on the Eastern Cooperative Oncology Group (ECOG) E2197 study, the 10-year rates of local recurrence were 3.2, 2.9, and 10.1 % for low, intermediate, and high RS (p=0.17); but was significantly associated with LRR when RS was evaluated as a continuous variable, (HR 2.66; P = 0.03) (Solin 2012). This supports that the RS represents a reliable means of stratifying HS breast cancer by prognosis
beyond the limits of standard clinical pathologic factors to identify a group that had a clinically acceptable LRR rate post lumpectomy without radiotherapy.

To address this clinical question, NRG Oncology Breast Committee submitted Concept 9584, A Randomized Phase III Trial of Adjuvant Radiotherapy versus Observation Following Lumpectomy in Patients with Biologically Low-Risk Hormone-Sensitive Stage I Breast Cancer Who Receive Endocrine Therapy in 2013. This concept proposed to test whether radiotherapy offers a substantial benefit in reducing breast cancer recurrence in patients with ER+, PR+, HER2- disease who have a low OncotypeDX™ recurrence score (< 18) and who receive lumpectomy and endocrine therapy. Given the EBCTCG meta-analysis findings (Clarke 2005, EBCTCG 2011), the concept design used as a primary endpoint of invasive or DCIS recurrence-free interval (RFI) to avoid missing the potential for increases in life threatening regional and distant metastases with omission of radiation. A non-inferiority design required an accrual of 2,068 patients. It was reviewed at the NCI Breast Cancer Local Regional Task Force (BOLD) and Breast Cancer Steering Committee (BCSC) and while assessed as consistent with the BCSC scientific priority of de-escalating breast cancer treatment in low risk populations, the large targeted accrual was a major barrier at the time and the concept was disapproved.

The NRG Breast Committee subsequently collaborated with the BOLD Task Force in an alliance with the Cancer Intervention, Surveillance Modeling Network (CISNET) Breast Cancer Working Group to determine if the trial outcome could be adequately modeled based on prior trial data, and if an improved, more efficient trial design could be discerned (Jayasekera 2018). This collaborative study sought to replicate the goals of the NRG 9584 Concept to determine the effect of breast radiotherapy on local-regional and distant recurrence, breast cancer-specific and all-cause mortality conditional on genomic risk assessments in a pooled analysis of breast cancer patients from seven clinical trials (EBCTCG 2011, Fyles 2004, Winzer 2010, Sparano 2015, Fisher 1989, Fisher 1997, Fisher 2002, Kunkler 2015, Blamey 2013, Potter 2007). The final sample included 1,778 patients from the seven clinical trials. Except for patients in the TAILORx study (20), there was no HER2 information, and the Oncotype Recurrence Scores (0-100) were imputed for the other six trials using a deterministic regression-based multiple imputation approach, and a population-based donor dataset with Oncotype DX™ recurrence scores (Jayasekera 2018). The imputation model included age, tumor size, tumor grade, ER/PR status, radiation, and HER2 status. The primary endpoint of the pooled analysis was recurrence-free interval (RFI), and included time from randomization/enrollment to any occurrence of local (invasive), regional, or distant recurrence, or death from breast cancer. Omission of radiotherapy significantly increased the risk of loco-regional recurrence events (adjusted HR: 3.9, 95% CI 1.8-8.4, 2p<0.01), but not the risk of distant recurrence or breast cancer death. At 5-years, the loco-regional RFI rate with radiotherapy was 98.6% compared to 93.7% without radiotherapy (absolute difference 4.9%, 95% CI 2.5-7.2%, 2p<0.01). At 10-years, the loco-regional RFI rate with radiotherapy was 96.6% compared to 85.5% without radiotherapy (absolute difference 11.1%, 95% CI 6.8-15.4%, 2p<0.01). A subset analysis demonstrated significantly more recurrences associated with age < 60 years and RS 11-18 (Jayasekera 2018). Overall, the results of the pooled analysis suggest that omission of radiotherapy after breast conservation in hormone-sensitive low-risk patients could lead to higher relative differences, but small absolute differences in RFI rates. Moreover, omission of radiotherapy did not appear to increase distant recurrences or early death in this low-risk population. As clinical decision-making is usually based on absolute differences, the conclusion was that future trials should focus on an acceptable absolute difference in local recurrence in its design.
2.3 There is Growing Clinical Interest to Reduce Breast Cancer Overtreatment with Radiation Therapy

There has been increasing clinical enthusiasm for evaluating the role of biomarkers to reduce overtreatment with radiotherapy by selecting low risk HS, node negative breast cancer patients for whom breast conservation is achievable with lumpectomy alone. This has led to several ongoing clinical trials (Table 1). In all cases, these trials include stage 1 breast cancer that is ER+, PR+, and HER2-negative that is low risk based on a biomarker. Most of these are single arm observation trials; and only the IDEA trial uses the RS as the discriminating biomarker. The EXPERT clinical trial that opened for accrual in August 2017 in Australia and New Zealand is the only randomized trial to date enrolling stage 1 HS, HER2-neg breast cancer that has a PAM50 ROR score < 60. The PAM50 is a 50-gene assay that sub-classes breast cancers into the 4 molecular subtypes (luminal A/B, basal like, and HER2). The Risk of Relapse (ROR) score includes the weighting of proliferation genes within molecular subtypes with/ without tumor size (Walden 2015). It has been demonstrated to be prognostic for local regional recurrence in archival samples from the ABCSG4 trial (Fitzal 2014). In the US, the RS has been used for > 10 years for systemic therapy decision making and is included in the NCCN guidelines since in 2008. The recent primary outcome report of the TAILORX clinical trial (Sparano 2018) that confirmed women > 50 years old with low risk RS, node negative, hormone sensitive breast cancer can safely omit chemotherapy from systemic therapy and can be treated solely with endocrine therapy likely solidifies the prevalence and predominance of RS use in clinical practice. For this reason, a trial to de-escalate radiotherapy in breast conservation using RS is timely as it can build on existing confidence and enthusiasm for the biomarker for guiding clinical decision and resonates with expanding clinical interest in radiation oncology to identify which breast conservation patients can safely be treated with lumpectomy alone.

Table 1. Clinical Trials evaluating BCT without radiation in hormone sensitive breast cancer

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<th>Biological Selection</th>
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<td>&gt; 50 years</td>
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<td>IDEA</td>
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<td>Phase II, single arm observation</td>
<td>RS &lt; 18</td>
<td>50-69 years</td>
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<td>PRECISION</td>
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<td>Phase II, single arm observation</td>
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<td>EXPERT</td>
<td>NCT02889874</td>
<td>Phase III randomized RT vs Observation</td>
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<td>PRIMETIME</td>
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</tbody>
</table>

Over 250,000 new diagnoses of invasive breast cancer are anticipated each year in the United States and roughly 50% of these are stage 1 (Fitzal 2014, Desantis 2017). From past registry analyses, approximately 60% of stage 1 cases undergo breast conservation and 75-80% receive breast radiotherapy (Desantis 2017, Sareigo 2008). Anticipating that 60-70% or more are hormone sensitive, a significant portion of these patients will undergo RS for systemic therapy decision making. An analysis of the SEER database linked to Genomic Health Clinical Laboratory RS results revealed that of those that had undergone RS testing, 89% were node negative, and 74.8% has a tumor size > 5 mm and < 20 mm in size (Petkov 2016). This supports that those tested with RS are the same population that should be targeted for reducing overtreatment with RT following BCS if the RS is low. The outcome of this proposed trial could allow as many as 25,000 breast cancer patients or more annually to safely omit breast radiotherapy after lumpectomy.
2.4 Patient Experience of De-escalating Breast Conserving Therapy to Lumpectomy without Radiation is Needed

An important aspect to successfully de-escalating treatment is patient acceptance of a major change in an established treatment paradigm like breast radiotherapy post lumpectomy. Patient reported outcomes (PROs) have been studied in clinical trial and observational data researching the question of mastectomy vs. breast conserving treatment with RT, but there is limited contemporary data on the impact of omission of RT. Two studies conducted by Hayman (Hayman 1997, Hayman 2005) provide some understanding of patient utilities for various health states after lumpectomy. In the case of invasive cancer, fear of a local recurrence and an actual local recurrence leading to mastectomy have such a negative impact on quality of life (QOL) that patients are willing to accept the risks and inconvenience of RT to avoid them (Hayman 1997).

In a subsequent study, Hayman et al. (Hayman 2005) interviewed 120 DCIS patients and 240 non-patient participants regarding time-trade off balance from RT after lumpectomy. As DCIS patients do not derive a survival benefit, the perceived value of RT depends on the trade-off between the fear and consequences of both noninvasive and invasive local recurrence versus the inconvenience and potential toxicity of RT. Few differences were found in exploring the preferences of patients with DCIS and the non-patients. Both had the lowest utilities for invasive local recurrence, regardless of the initial treatment or manner of salvage therapy (Hayman 2005).

Further information about the patient experience after treatment of breast cancer is available from a series of studies conducted by Stephen Katz and his team (Katz 2005) examining several thousand patients with DCIS and invasive breast cancer recruited from the Los Angeles and Detroit Surveillance, Epidemiology and End Results (SEER) registries. Using rapid case ascertainment, these investigators surveyed women about their QOL, decision-making regarding treatments, as well as worry about recurrence about 7 months after diagnosis. In multivariate models, there was no difference in PROs by breast cancer stage (DCIS vs. invasive) (Janz 2007).

In an examination of post-treatment symptoms, DCIS patients did not differ from those with invasive cancer (e.g. breast and arm symptoms, pain, treatment side effects), and only sleep was a greater problem for patients with invasive disease (Janz 2007). Finally, in an analysis that examined worry about recurrence in this patient sample (Janz 2011), the authors focused on worry about the cancer returning to the same breast, occurring in the other breast, or spreading to other parts of the body. Factors significantly associated with greater worry were race/ethnicity, younger age, being employed, more pain and fatigue, and RT. Latinas were at greatest risk of worry followed by white women and African American women in this sample (Janz 2011). Of note, stage of disease (DCIS vs. invasive) did not influence worry about recurrence.

In recent years, trends in local treatment for breast cancer demonstrate that women select overtreatment with contralateral prophylactic mastectomy in addition to mastectomy for their low risk stage 1 breast cancer for, “peace of mind” (Rosenberg 2013). In addition, women with low risk disease facing breast cancer treatment decisions overestimate their future risks (Kaiser 2019) representing another potential barrier to reducing overtreatment. This emphasizes the importance of understanding the patient experience to be successful in de-escalating radiotherapy after lumpectomy for HS stage 1, RS low risk cases. There is a critical need for this information so patients can make informed decisions. The quality of life questions will include a focus on worry about recurrence.

Another important consideration is breast pain. As detailed in the quality of life section, the long-term follow-up of the randomized Swedish SWEBCG91-RT trial (Lundstedt 2010) suggested durable differences in pain experienced by women randomized to RT, even 10-17 years after treatment. Differences in breast pain have also been documented in the U.S. CALGB 9343 randomized trial, with physician reports of pain only being higher during the first year only but patient-reported breast pain being higher for all four years of follow-up (Hughes 2004).
Canadian OCOG randomized trial, RT was associated with being troubled by breast pain, with the difference most pronounced at 6 months after randomization, and decreased by two years. Differences in chronic pain have also been suggested by studies from Denmark (Tasmuth 1995, Tasmuth 1997, Peuckmann 2009). Further information about breast pain after radiotherapy delivered with modern techniques is important, as pain is a meaningful experience for patients making decisions in this context, and this trial offers an opportunity to measure this directly over time.

We also have the opportunity to measure other experiences and outcomes of importance to patients. This includes global quality of life as well as breast-specific outcomes that are more likely to vary by treatment arm, such as the cosmetic appearance of the breast. Evaluation of cosmetic outcome from different methods of radiation, such as hypo fractionation and accelerated partial breast irradiation have demonstrated minimal differences (Ganz 2019; White 2019). Few studies have evaluated the cosmetic outcome changes from breast radiation compared to lumpectomy alone. Information regarding appearance of the breast with and without radiation for breast conservation may be essential to patients when deciding about trade-offs for undergoing radiation therapy. Patient’s evaluation of the cosmetic outcome of the treated breast remains of primary importance and collected through validated patient reported outcome measures.

2.5 Efforts are Needed to Ensure that Reducing Overtreatment with Radiation does not Reduce the Likelihood of Breast Conservation

Patients with early stage breast cancer choosing breast conservation treatment are motivated by the desire to preserve their natural breast without compromising their survival outcomes. A barrier to reducing overtreatment may be concern on the part of patients and physicians about the impact of local recurrence on the probability of ultimate breast preservation. Few data are available to guide management decisions at the time of local recurrence or to reassure patients and their physicians about anticipated outcomes. The standard treatment of in-breast cancer recurrence after lumpectomy and breast radiotherapy has been mastectomy. In examining the limited existing data, mastectomy is used for management of in-breast recurrence after a first breast preserving treatment with or without radiation. An analysis of practice patterns for treatment of local recurrence after a first breast conservation for DCIS in the NCCN Oncology Outcomes Database and the HMO Cancer Research Network (CRN) demonstrated a second breast conservation rate of only 37% and 48%, respectively, for lower risk breast cancer even when there was no prior RT delivered (Greenberg 2014). Similarly, Rakovitch et al evaluated the Ontario Cancer Registry including 3303 women with DCIS; 50% underwent lumpectomy alone and the other 50% received RT (Rakovitch 2018). Mastectomy was used to treat LR in 57.4% of women who recurred after BCS alone. Women treated with upfront lumpectomy and RT had higher rates of bilateral breast preservation at 10 years compared to those treated by lumpectomy alone (87.3% vs. 82.7%, p = 0.0096). Even in elderly women with HS, node-negative stage I breast cancer in the PRIME 2 trial, 50% of local recurrences following lumpectomy without radiation underwent mastectomy (Kunkler 2015). This trial could provide valuable information in understanding treatment patterns for salvage of local recurrence after a first lumpectomy without radiation and the impact on overall rate of breast preservation.

2.6 Adherence to Endocrine Therapy may be a Critical Factor for Optimizing Use of Radiotherapy after Breast Conserving Surgery.

For early stage hormone sensitive breast cancer, the addition of endocrine therapy reduces the risk of IBTR after breast conserving surgery with or without breast radiotherapy (Winzer 2010, Blamey 2013, Mamounas 2010). In the German Breast Group V trial, breast conserving surgery and tamoxifen alone resulted in similar event rates as the addition of radiotherapy alone (Winzer 2010). In the BASO II trial, receipt of both tamoxifen and radiotherapy had a highly significant
protective effect on IBTR (P<0.001) with no IBTR events occurring compared to BCS alone in which IBTR rate was 1.9% per year. In addition, tamoxifen alone resulted in a significantly lower risk of IBTR than BCS alone, p=0.003 (Blamey 2013). Given these findings, patient adherence to endocrine therapy may then be a critical factor for measuring whether IBTR from breast conserving surgery without radiation is non inferior to breast conserving surgery with radiation. Disproportionate non adherence or discontinuation of endocrine therapy in one arm over the other could alter the incidence of IBTR in either arm of the trial confounding the treatment arm effect. Intention to take at least 5 years of endocrine therapy is an eligibility criterion for this trial. Yet, actual adherence to endocrine therapy throughout its duration can change. Hershman et al. reported that among 8769 breast cancer patients prescribed either adjuvant tamoxifen or an AI for early stage breast cancer and who filled at least one prescription, 32% had discontinued therapy by 4.5 years, and of those who continued, 72% were fully adherent (Hershman 2010). Of note, receipt of radiation trended towards less discontinuation and non-adherence. A different pattern was seen on the NRG RTOG 9804 clinical trial that randomized patients with ductal carcinoma in situ (DCIS) post lumpectomy to breast radiation or observation without radiation. Intention to use tamoxifen was indicated at study entry for 69% of patients, balanced equally between treatment arms. However, actual receipt as documented in the medical record was significantly different between arms with more use in those randomized to observation (66%) versus those who received breast radiation (58%) (p=0.05) (McCormick 2018). Discontinuation and non-adherence were not specifically measured over the duration of the trial.

There are numerous methods for measuring adherence to adjuvant endocrine therapy that have been used on clinical trials including pill counts, patient report with diaries or questionnaires, medication refill counts, among others (Osterberg 2005). Pill counts are not feasible on this trial as endocrine therapy will be prescribed per their treating oncologists. Patient reports will be requested at each follow up visit but this use is susceptible to error with increases in time between visits and results can be distorted by the patient. Medication refill counts is objective and easy to obtain. While prescription refill is not equivalent to ingestion of medication it can be used to support patient reports. Electronic prescribing (e-prescribing) makes monitoring prescription refills achievable through review of the electronic medical records. Becker Hospital Review reported that by 2018, 84% of oncologists used e-prescribing for outpatient medications (Becker Hospital Review 2020).

2.7 To Determine a Machine Learning/Artificial Intelligence Algorithm for Radiotherapy Quality Assurance on Arm 1

An important secondary endpoint of this trial is to assess the patient’s experience with radiation treatment that will be compared and contrasted to those who do not receive radiation. In particular patient reported toxicities, such as pain and long term effects on the breast appearance related to radiation will be studied. Therefore, within the radiation treated arm it will be important to follow radiation quality to determine its effects on these outcomes. There are known radiation delivery approaches that improve quality and reduce toxicity such as limiting dose to normal tissue, (e.g., lung, heart, and contralateral breast) and minimizing dose heterogeneity across the breast clinical target volume. To improve and reduce variation that can occur when quality reviews are performed by multiple investigators, a machine learning algorithm that will be used to perform the QA of the RT plans is proposed.

2.8 Collection of Tissue and Blood for Future Translational Research

Blood and tissue samples will be banked for correlative studies to identify gene expressions and/or mutations associated with breast recurrence and predictive of radiation toxicity.
3.0  ELIGIBILITY AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Clinical Coordinating Department (CCD [see protocol cover page]). For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

3.1  Patient Pre-Entry and Randomization

For the NRG-BR007 study, patients with a T1a tumor (≤0.5 cm in size) who do not have an Oncotype DX Recurrence Score must have a tissue sample sent to Genomic Health for a Recurrence Score to determine eligibility. For these patients, Genomic Health will cover the cost of the test.

3.1.1  Pre-Entry (ALL patients)

- Step 1: All patients will have to be registered in NRG-BR007 before being randomized.
- The authorized site staff must obtain a signed consent form from the potential patients before any study specific procedures are performed.
- The authorized site staff must determine patient eligibility. See Sections 3.2 and 3.3.
- During Pre-Entry in OPEN, patients will be assigned a unique patient identifier which will be used to identify the sample to be sent for central Oncotype DX Recurrence Score testing (for patients with a T1a tumor (≤0.5 cm in size) who have not had a Recurrence Score), the eCRFs in Medidata RAVE, and any other trial-related communications. See Section 10.0 and the NRG-BR007 Pathology and Correlative Science Instructions for ordering the Oncotype DX Recurrence Score test.
- Patients who already have a Recurrence Score result of ≤ 18, will be registered in Step 1 and go straight to randomization in Step 2.
- When a Recurrence Score result of ≤ 18 is received on central testing for patients with a T1a tumor (≤ 0.5 cm in size), the patient should be randomized. Patients who do not have a Recurrence Score result of ≤ 18 by central testing will not be randomized, will be treated per investigator discretion, and will not be followed on BR007.

3.1.2  Randomization (ALL patients)

- Step 2: If a patient meets all eligibility requirements, the authorized site staff will randomize the patient using OPEN.
- OPEN will randomly assign treatment (breast radiation therapy + endocrine therapy or no breast radiation + endocrine therapy).

3.2  Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.2.1  The patient or a legally authorized representative must provide study-specific informed consent prior to study entry and, for patients treated in the U.S., authorization permitting release of personal health information.
3.2.2 The patient must be ≥ 50 years and < 70 years of age.

3.2.3 The trial is open to female and male patients.

3.2.4 The patient must have an ECOG performance status of 0 or 1.

3.2.5 The patient must have undergone a lumpectomy and the margins of the resected specimen or re-excision must be histologically free of invasive tumor and DCIS with no ink on tumor as determined by the local pathologist. If pathologic examination demonstrates tumor at the line of resection, additional excisions may be performed to obtain clear margins. (Patients with margins positive for LCIS are eligible without additional resection.)

3.2.6 The tumor must be unilateral invasive adenocarcinoma of the breast on histologic examination.

3.2.7 Patient must have undergone axillary staging (sentinel node biopsy and/or axillary node dissection).

3.2.8 The following staging criteria must be met postoperatively according to AJCC 8th edition criteria:
   - By pathologic evaluation, primary tumor must be pT1 (≤ 2 cm).
   - By pathologic evaluation, ipsilateral nodes must be pN0. (Patients with pathologic staging of pN0(i+) or pN0(mol+) are NOT eligible.)

3.2.9 Oncotype DX Recurrence Score of ≤ 18 on diagnostic core biopsy or resected specimen.**

** For patients with a T1a tumor (≤ 0.5 cm in size) who do not already have an Oncotype DX Recurrence Score at study entry, a specimen (unstained blocks or slides) must be sent to the Genomic Health centralized laboratory.

3.2.10 The tumor must have been determined to be ER and/or PgR positive assessed by current ASCO/CAP Guideline Recommendations for hormone receptor testing. Patients with ≥ 1% ER or PgR staining by IHC are considered positive.

3.2.11 The tumor must have been determined to be HER2-negative by current ASCO/CAP guidelines.

3.2.12 Patients may be premenopausal or postmenopausal at the time of study entry. For study purposes, postmenopausal is defined as:
   - Age 56 or older with no spontaneous menses for at least 12 months prior to study entry; or a documented hysterectomy; or
   - Age 55 or younger with no spontaneous menses for at least 12 months prior to study entry (e.g., spontaneous or secondary to hysterectomy) and with a documented estradiol level in the postmenopausal range according to local institutional/laboratory standard; or
   - Documented bilateral oophorectomy.

3.2.13 The interval between the last surgery for breast cancer (including re-excision of margins) and study entry must be no more than 70 days.

3.2.14 The patient must have recovered from surgery with the incision completely healed and no signs of infection.

3.2.15 Bilateral mammogram or MRI within 6 months prior to study entry.

3.2.16 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.2.17 Patients must be intending to take endocrine therapy for a minimum 5 years duration (tamoxifen or aromatase inhibitor). The specific regimen of endocrine therapy is at the treating physician’s discretion.
3.3 **Ineligibility Criteria**

*Patients with any of the following conditions are NOT eligible for this study.*

3.3.1 Definitive clinical or radiologic evidence of metastatic disease.
3.3.2 pT2 - pT4 tumors including inflammatory breast cancer.
3.3.3 Pathologic staging of pN0(i+) or pN0(mol+), pN1, pN2, or pN3 disease.
3.3.4 Patient had a mastectomy.
3.3.5 Palpable or radiographically suspicious ipsilateral or contralateral axillary, supraclavicular, infraclavicular, or internal mammary nodes, unless there is histologic confirmation that these nodes are negative for tumor.
3.3.6 Suspicious microcalcifications, densities, or palpable abnormalities (in the ipsilateral or contralateral breast) unless biopsied and found to be benign.
3.3.7 Non-epithelial breast malignancies such as sarcoma or lymphoma.
3.3.8 Proven multicentric carcinoma (invasive cancer or DCIS) in more than one quadrant or separated by 4 or more centimeters. (Patients with multifocal carcinoma are eligible.)
3.3.9 Paget's disease of the nipple.
3.3.10 Any history, not including the index cancer, of ipsilateral invasive breast cancer or ipsilateral DCIS treated or not treated. (Patients with synchronous or previous ipsilateral LCIS are eligible.)
3.3.11 Synchronous or previous contralateral invasive breast cancer or DCIS. (Patients with synchronous and/or previous contralateral LCIS are eligible.)
3.3.12 Surgical margins that cannot be microscopically assessed or are positive at pathologic evaluation. (If surgical margins are rendered free of disease by re-excision, the patient is eligible.)
3.3.13 Treatment plan that includes regional nodal irradiation.
3.3.14 Any treatment with radiation therapy, chemotherapy, biotherapy, and/or endocrine therapy administered for the currently diagnosed breast cancer prior to study entry. (Short course endocrine therapy of < 6 weeks duration is acceptable post core biopsy pre surgery if the Oncotype DX Recurrence Score is assessed on the biopsy core and is ≤ 18.)
3.3.15 History of non-breast malignancies (except for in situ cancers treated only by local excision and basal cell and squamous cell carcinomas of the skin) within 5 years prior to study entry.
3.3.16 Current therapy with any endocrine therapy such as raloxifene (Evista®), tamoxifen, or other selective estrogen receptor modulators (SERMs), either for osteoporosis or breast cancer prevention. (Short course endocrine therapy of < 6 weeks duration is acceptable post core biopsy pre surgery if the Oncotype DX Recurrence Score is assessed on the biopsy core and is ≤ 18.)
3.3.17 Patients intending to continue on oral, transdermal, or subdermal estrogen replacement (including all estrogen only and estrogen-progesterone formulas) are not eligible. Patients that discontinue oral, transdermal, or subdermal estrogen replacement prior to registration are eligible.
3.3.18 Prior breast or thoracic RT for any condition.
3.3.19 Active collagen vascular disease, specifically dermatomyositis with a CPK level above normal or with an active skin rash, systemic lupus erythematosis, or scleroderma.
3.3.20 Pregnancy or lactation at the time of study entry or intention to become pregnant during treatment. *Note: Pregnancy testing according to institutional standards for women of childbearing potential must be performed within 2 weeks prior to study entry.*

3.3.21 Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of study therapy or that may affect the interpretation of the results or render the patient at high risk from treatment complications.

3.3.22 Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements or interfere with interpretation of study results.

3.3.23 Use of any investigational product within 30 days prior to study entry.
# 4.0 REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

Table 2. Tests, exams, and other requirements prior to study entry and randomization

<table>
<thead>
<tr>
<th>Required Assessments</th>
<th>Prior to Study entry/Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent form signed by the patient</td>
<td>X</td>
</tr>
<tr>
<td>Confirm Oncotype DX Recurrence Score ≤ 18(^a)</td>
<td>X</td>
</tr>
<tr>
<td>Central testing for Oncotype DX Recurrence Score <em>for patients with T1a tumors (≤ 0.5 cm in size) without a Recurrence Score</em>(^a)</td>
<td>After study entry but before randomization</td>
</tr>
<tr>
<td>Determination of hormone receptor status <em>(Section 3.1.10)</em></td>
<td>X</td>
</tr>
<tr>
<td>Determination of HER2 status <em>(Section 3.1.11)</em></td>
<td>X</td>
</tr>
<tr>
<td>Menopausal status <em>(Section 3.1.12)</em></td>
<td>X(^b)</td>
</tr>
<tr>
<td>History &amp; physical exam</td>
<td>X(^c) Within 12 weeks</td>
</tr>
<tr>
<td>Assessment of performance status <em>(Appendix A)</em></td>
<td>X</td>
</tr>
<tr>
<td>Height &amp; weight</td>
<td>X</td>
</tr>
<tr>
<td>CBC/differential/platelet count</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>X(^d) Within 2 weeks</td>
</tr>
<tr>
<td>Bilateral breast imaging (Mammogram or MRI)</td>
<td>X(^e) Within 6 months</td>
</tr>
<tr>
<td>Staging imaging</td>
<td>X(^f)</td>
</tr>
<tr>
<td>Health-Related Quality of Life (HRQOL) questionnaire</td>
<td>X(^g)</td>
</tr>
<tr>
<td>Collection and submission of optional blood specimen</td>
<td>X(^h) Before or after randomization (before therapy begins)</td>
</tr>
</tbody>
</table>

\(^a\) Per NCCN 2019 guidelines, an Oncotype DX RS is indicated for breast cancers greater than 0.5 cm in size and this can be ordered by any of the patient’s providers including surgeon, medical oncologist, and radiation oncologist. For patients with T1a (≤ 0.5 cm in size) tumors who do not have a RS and are otherwise eligible, a tissue sample will be sent to Genomic Health for determining the Oncotype DX RS. Patients with an Oncotype DX RS < 18 are eligible for enrollment (See Section 3.1).

\(^b\) Menopausal status at the time of breast cancer diagnosis.

\(^c\) Complete H&P by physician or other healthcare professional.

\(^d\) For women of childbearing potential: Pregnancy testing must be performed according to institutional standards.

\(^e\) Ultrasound is not a permissible substitute for either a mammogram or MRI.

\(^f\) Staging imaging is not required but if performed as part of clinical care must not show any definitive radiologic evidence of metastatic disease. Imaging studies should be performed if clinically indicated at the investigator's discretion.

\(^g\) For patients who agree to participate in the HRQOL study, the HRQOL questionnaire must be administered after the informed consent is signed but before study entry (see Section 11.0). For HRQOL reporting, this study uses Medidata Patient Cloud ePRO. Remember to register the patient to the Patient Cloud ePRO. For instructions on registering the patient, please refer to Appendix D.

\(^h\) *Requirement for all patients who agreed to optional blood collection and submission* in the consent form. See Section 10.0 and the NRG-BR007 Pathology and Correlative Science Instructions.
<table>
<thead>
<tr>
<th>Required assessments (see footnote a)</th>
<th>After randomization</th>
<th>End of RT(+-3 days) or 3 months from randomization (see footnote b)</th>
<th>30 days after the last dose of RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>History &amp; physical exam&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Breast assessment/exam</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Adverse event assessment</td>
<td></td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bilateral breast imaging (Mammogram or MRI)</td>
<td>See footnote e</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection and submission of optional blood&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Optional tumor block submission&lt;sup&gt;g&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**a** History and physical, and other testing may be performed more frequently at the discretion of the investigator.

**b** Patients in Arm 1 will have exams and assessments at the end of RT. (End of RT +/-3 business days from the last treatment). **Patients in Arm 2 will have exams and assessments at 3 months after randomization.**

**c** Updated H&P with exams (by physician or other healthcare professional) appropriate for therapy-related assessments and follow-up evaluations.

**d** An adverse event assessment at end of RT and a final adverse event assessment 30 days after the last dose of radiation therapy must be done for patients in Group Arm 1 and at 3 months after randomization for patients in Arm 2; assessment may be based on office notes from other physician visits or telephone contact with the patient.

**e** Mammogram or MRI is required. First mammogram will be 1 year from the most recent mammogram (or MRI) performed prior to randomization and then every 12 months. (Mammograms may be performed more frequently at the discretion of the investigator.)

**f** **Requirement for all patients who agreed to optional blood collection and submission** in the consent form. See Section 10.0 and the NRG-BR007 Pathology and Correlative Science Instructions.

**g** Submission of blocks from the primary breast tumor within 90 days following randomization are **required for all patients who agreed to optional tissue submission** in the consent form. See Section 10.0 and the NRG-BR007 Pathology and Correlative Science Instructions.

**NOTE**: Tests, exams, and assessments, are **not required** following a documented invasive breast cancer recurrence, invasive contralateral breast cancer, or second nonbreast primary cancer excluding squamous or basal cell skin cancers or new in situ carcinomas of any site. Follow-up for subsequent cancer events and for survival continues to be required every 6 months through 24 months and then every 12 months from Year 3 through Year 10. (See Section 7.0 for adverse event reporting requirements.)
Table 4. Tests, exams, and other requirements after therapy for Arm 1 and Arm 2

<table>
<thead>
<tr>
<th>Required assessments (see footnote a)</th>
<th>6 and 12 months from randomization</th>
<th>18 and 24 months from randomization</th>
<th>Years 3 through 10 from randomization (every 12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History &amp; physical examb</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Breast assessment/exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse event assessmentc</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cardiac toxicity assessmentd</td>
<td>X (12 months only)</td>
<td>X (24 months only)</td>
<td>X</td>
</tr>
<tr>
<td>Bilateral breast imaging (Mammogram or MRI)</td>
<td>Xe (24 months only)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HRQOL questionnaire</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Collection and submission of optional blood f</td>
<td>X (12 months only)</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

a  History and physical, and other testing may be performed more frequently at the discretion of the investigator.
b  Updated H&P with exams (by physician or other healthcare professional) appropriate for therapy-related assessments and follow-up evaluations.
c  An adverse event assessment at 6, 12, 18, and 24 months from randomization and every 12 months from years 3 through 10 from randomization as noted in Section 7.6.2; assessment may be based on office notes from other physician visits or telephone contact with the patient.
d  Report late cardiac toxicity information (≥ grade 2 cardiac toxicity), annually through Year 5 within the BR007 Follow-up folder in Medidata Rave as noted in Section 7.8.
e  Mammogram or MRI is required. First mammogram will be 1 year from the most recent mammogram (or MRI) performed prior to randomization and then every 12 months. (Mammograms may be performed more frequently at the discretion of the investigator.)
f  Requirement for all patients who agreed to optional blood collection and submission in the consent form. See Section 10.0 and the NRG-BR007 Pathology and Correlative Science Instructions.

NOTE: Tests, exams, and assessments, are not required following a documented invasive breast cancer recurrence, invasive contralateral breast cancer, or second nonbreast primary cancer excluding squamous or basal cell skin cancers or new in situ carcinomas of any site. Follow-up for subsequent cancer events and for survival continues to be required every 6 months through 24 months and then every 12 months from Year 3 through Year 10. (See Section 7.0 for adverse event reporting requirements.)
5.0 TREATMENT PLAN/REGIMEN DESCRIPTION

5.1 Treatment Regimen

5.1.1 ARM 1: Radiation Therapy and Endocrine Therapy

- Post lumpectomy radiation therapy will be external beam radiation to either the whole breast + boost, partial breast irradiation, or Accelerated Partial Breast Irradiation as outlined in Section 5.4 that must begin within 12 weeks of the last breast cancer surgery (including re-excision of margins).

- Endocrine therapy for a minimum of 5 years. The specific regimen of endocrine therapy is at the treating physician's discretion. The dose and schedule of the drug(s) used for endocrine therapy should be consistent with the instructions in the drug package insert(s). Endocrine therapy may be initiated before, during, or after completion of radiation therapy at the discretion of the investigator.

5.1.2 ARM 2: Endocrine Therapy Only

Endocrine therapy for a minimum of 5 years. The specific regimen of endocrine therapy is at the treating physician's discretion. The dose and schedule of the drug(s) used for endocrine therapy should be consistent with the instructions in the drug package insert(s).

5.2 Breast Surgery (ARM 1 and ARM 2)

Lumpectomy or oncoplastic lumpectomy are permitted. The final surgical margins must be negative (no ink on tumor) per SSO-ASTRO guidelines (Moran 2014)

Salvage surgery for in-breast tumor recurrence: For patients assigned to ARM2 post lumpectomy endocrine therapy only and experience an in-breast tumor recurrence (IBTR) event, the preferred surgical treatment is a second breast conserving surgery when feasible and postoperative breast irradiation. Documentation of salvage treatment for IBTR will be collected with specifics addressing rationale of why a second breast conservation was not performed.

5.3 Endocrine Therapy (ARM 1 and ARM 2):

- Selection of endocrine therapy from below will be at the investigator's discretion. The dose and schedule of endocrine therapy should be consistent with the drug package insert.
  - Tamoxifen 20 mg daily
  - Anastrozole 1 mg daily
  - Letrozole 2.5 mg daily
  - Exemestane 25 mg daily

- LHRH agonist/antagonists (e.g., Lupron® and Zoladex®) or ovarian ablation by surgery or RT are permitted for premenopausal patients. Histrelin is not permitted to be used in this study.

- Endocrine therapy may be initiated before, during, or after completion of radiation therapy at the discretion of the investigator.
5.4 Radiation Therapy (ARM 1)

Radiation therapy for patients randomized to Arm 1 can be per standard of care practices for either whole breast irradiation (WBI), accelerated partial breast irradiation (APBI) or partial breast irradiation (PBI). Hypo- or conventional fractionated whole breast irradiation with or without a lumpectomy boost, is allowed. The following are not permitted: Boost in patients being treated with partial breast techniques, brachytherapy or IORT methods, treatment of regional nodes, proton therapy, and bolus.

5.4.1 Dose Recommendations for Standard of Care Radiation Therapy

- **Whole Breast Irradiation:**
  - Breast: 42.56 Gy in 16 fractions of 2.66 Gy q day
  - 40 Gy in 15 fractions of 2.67 Gy q day
  - 50 Gy in 25 fractions of 2 Gy q day
  - Sequential Boost: 10 Gy in 5 - 4 fractions of 2.0-2.5 Gy

- **Accelerated Partial Breast Irradiation:**
  - Lumpectomy PTV eval: 38.50 Gy in 10 fraction of 3.85 Gy BID with minimum of 6-7 hours between each fraction
  - Lumpectomy PTV eval: 30 Gy in 5 fractions of 6 Gy delivered every other day

- **Partial Breast Irradiation**
  - Lumpectomy PTV eval: 40 Gy in 15 fractions of 2.67 Gy q day

5.4.2 Treatment Delivery

This protocol requires contour based CT treatment planning and documentation of dose volume analysis (DVA) of dose to targets and organs at risk. A composite CT dose plan and DVA of the entire prescribed dose for WBI + boost, APBI, and PBI will be submitted for Quality Assurance (Section 5.4.11). Standard of care radiation delivery methods and techniques with photons and electrons for breast irradiation are to be used per the discretion of the treating physician.

5.4.2.1 All 3D-CRT and IMRT techniques including Tomotherapy and VMAT are allowed.

5.4.2.2 Boost to the lumpectomy PTV eval following WBI is per the discretion of the treating physician. If a lumpectomy boost is utilized, a composite dose plan of the entire prescribed dose for both the WBI and boost treatment plans is recommended to be generated from the same CT prior to the start of treatment. When necessary, boost plans requiring re-simulation due to seroma size or other anatomical changes are also permitted. Composite treatment plans of whole breast and boost will be collected for Quality Assurance (Section 5.4.11)

5.4.2.3 The following radiation methods and techniques are not permitted:
- Brachytherapy or IORT
- Proton therapy
- Regional nodal irradiation
- Boost in patients receiving APBI or PBI
- Bolus
5.4.3 Immobilization and Simulation

5.4.3.1 Immobilization and Patient Position

Proper immobilization is critical and patient setup reproducibility must be achieved using appropriate clinical devices.

The patient may be positioned supine, prone, or in a lateral decubitus position as appropriate for patient comfort, sparing of organs at risk (OARs), or access to the target volumes, as long as composite CT dose plan and DVA is achievable that can be submitted for Quality Assurance.

5.4.3.2 CT Simulation

Planning CT scan in the treatment position will be required and will be used to define the clinical target volumes (CTV), planning target volumes (PTV), and OARs. Prior to simulation, radio-opaque wires are recommended to be placed upon the lumpectomy scar and clinical extent of the ipsilateral or targeted breast. The field of view (FOV) and superior-inferior extent of the CT simulation shall be large enough so as to encompass the target volumes, the entirety of the OARs (and specifically whole lungs and heart), and any regions through which treatment beams may enter or exit through the patient. This typically extends from the mandible superiorly to the below the lung costophrenic angles inferiorly. Other imaging modalities may be used to delineate target volumes and/or OARs, but dose calculation must be CT-based. External skin localizing marks, which may include permanent tattoos, are strongly recommended for radiation daily localization and set-up accuracy.

5.4.3.3 Breathing Control for Avoidance of OAR:

Respiratory motion management is allowed on this study including four-dimensional computed tomography (4DCT), active breath-hold, deep inspiration breath hold (DIBH), active breathing control (ABC), and gated breathing as means of reducing dose to heart and lung.

Respiratory-correlated images should be acquired during simulation to facilitate phase-specific gated radiation therapy or breath-hold radiation therapy, subject to the requirements and restrictions of the protocol. If a 4D simulation is performed, the respiratory phase-specific image (e.g., end-inhalation, end-exhalation, or intermediate phase) or specific 4D projection image (e.g., average intensity projection, maximum intensity projection) to be used as the primary planning image and/or for target-volume definition purposes shall be indicated. If a breath hold simulation is performed, reproducibility of the breath hold image acquisition and consistency of the breath hold position between simulation and treatment shall be established.

5.4.4 Definition of Target Volumes and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as “Required” in the table must be contoured and submitted with the treatment plan. Each of the target volume labels shall be appended with “_R” or “_L” to indicate whether the treated volume is right-sided or left-sided, respectively. Structures marked as “Required when applicable” must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. The treating physician must provide the target volumes and must verify the OAR contours.
For each of the treated volumes, the contour labels, description of the target, delineation guidelines, and validation requirements are tabulated below. These target volumes are adapted from RTOG 1005 and NSABP B-51/RTOG 1304. Validation may either be Required, Required when applicable, or Optional:

<table>
<thead>
<tr>
<th>Standard Name</th>
<th>Description</th>
<th>Delineation guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV_Lump</td>
<td>gross tumor volume (GTV) for Lumpectomy</td>
<td>Contour the lumpectomy bed as apparent on planning image. Use surgical clips or fiducials when present. Can include the excision cavity volume, architectural distortion, seroma.</td>
</tr>
<tr>
<td>CTV_Lump</td>
<td>lumpectomy CTV; CTV including regions of the GTV suspicious for subclinical disease</td>
<td>Include the lumpectomy GTV plus 1.0 cm to 1.5 cm of surrounding breast tissue, but exclude the pectoralis muscle, all chest wall muscles, ribs, contralateral breast, and regions exterior to the patient surface. For APBI 1.5 cm expansion on GTV recommended.</td>
</tr>
<tr>
<td>PTV_Lump</td>
<td>lumpectomy PTV</td>
<td>lumpectomy CTV + 0.5 cm (if IGRT used) or 0.7 cm (if no IGRT) expansion in all directions; exclude heart and lung</td>
</tr>
<tr>
<td>PTV_Lump_EVA</td>
<td>PTV evaluation volume; PTV minus overlapping critical structure ROIs; relevant regarding boosts to the lumpectomy site</td>
<td>recede PTV_Lump by 0.3 to 0.5 cm distal to the skin surface, do not extend beyond breast tissue, and do not cross midline</td>
</tr>
<tr>
<td>CTV_WB</td>
<td>whole breast CTV; ipsilateral (to be treated) breast</td>
<td>include the glandular breast tissue as apparent on the planning image, incorporating the anatomic borders as summarized in Appendix C and include the entire lumpectomy CTV</td>
</tr>
<tr>
<td>PTV_WB</td>
<td>whole breast PTV; ipsilateral (to be treated) breast</td>
<td>whole breast CTV + 0.5 cm (if IGRT used) or 0.7 cm (if no IGRT) 3D expansion and include entire lumpectomy PTV ; exclude heart and lung; do not cross midline</td>
</tr>
<tr>
<td>PTV_WB_EVA</td>
<td>whole breast PTV evaluation volume; ipsilateral (to be treated) breast</td>
<td>recede PTV_WB by 0.3 to 0.5 cm distal to the skin surface</td>
</tr>
</tbody>
</table>

**Detailed Specifications:**

Target volumes: The definitions of volumes used in this protocol generally conform to the NRG RTOG-endorsed consensus guidelines for delineation of target and normal structures for breast cancer [https://www.nrgoncology.org/Portals/0/Scientific%20Program/CIRO/Atlases/BreastCancerAtlas_corr.pdf](https://www.nrgoncology.org/Portals/0/Scientific%20Program/CIRO/Atlases/BreastCancerAtlas_corr.pdf) and the 1993 International Commission on Radiation Units and Measurements (ICRU) Report #50: Prescribing, Recording And Reporting Photon Beam Therapy. Using these consensus definitions for a guideline, target volume contours may vary some to fit the individual, specific case according to the treating physician’s judgment.
The general anatomic boundaries of the breast contours, along each of the superior-inferior, anterior-posterior, and lateral-medial directions, are tabulated below:

Table 6. Delineation guidelines for the breast

<table>
<thead>
<tr>
<th>Target volume label</th>
<th>Superior</th>
<th>Inferior</th>
<th>Anterior</th>
<th>Posterior</th>
<th>Lateral</th>
<th>Medial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast_L (left sided treatment) or Breast_R (right sided treatment)</td>
<td>clinical reference + second rib insertion</td>
<td>clinical reference + loss of image-apparent breast (inframammary fold)</td>
<td>skin</td>
<td>excludes pectoralis muscles, chest wall muscles, ribs</td>
<td>clinical reference + midaxillary line (typically), excludes latissimus (lat.) dorsi muscle</td>
<td>sternum-rib junction</td>
</tr>
</tbody>
</table>

Note: Borders are highly variable, depending upon breast size, amount of ptosis, and patient position.

5.4.5 Definition of Critical Structures and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as “Required” in the table must be contoured and submitted with the treatment plan. Structures marked as “Required when applicable” must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Table 7. Validation guidelines for organs at risk

<table>
<thead>
<tr>
<th>Standard Name</th>
<th>Description</th>
<th>Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung_R</td>
<td>right lung</td>
<td>Required</td>
</tr>
<tr>
<td>Lung_L</td>
<td>left lung</td>
<td>Required</td>
</tr>
<tr>
<td>Heart</td>
<td>heart</td>
<td>Required</td>
</tr>
<tr>
<td>Breast_L</td>
<td>left breast</td>
<td>Required</td>
</tr>
<tr>
<td>Breast_R</td>
<td>right breast</td>
<td>Required</td>
</tr>
<tr>
<td>Spinal_Cord</td>
<td>spinal cord</td>
<td>Required</td>
</tr>
<tr>
<td>External</td>
<td>patient skin surface</td>
<td>Required</td>
</tr>
</tbody>
</table>
**Detailed Specifications:**

The anatomic boundaries of the heart and lung, along each of the superior-inferior, anterior-posterior, and lateral-medial directions, are tabulated below:

Table 8. Delineation guidelines for organs at risk

<table>
<thead>
<tr>
<th>Organ at risk</th>
<th>Superior</th>
<th>Inferior</th>
<th>Anterior</th>
<th>Posterior</th>
<th>Lateral</th>
<th>Medial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast_R (left sided treatment) or Breast_L (right sided treatment)</td>
<td>clinical reference + second rib insertion</td>
<td>clinical reference + loss of image-apparent breast</td>
<td>skin</td>
<td>excludes pectoralis muscles, chest wall muscles, ribs</td>
<td>clinical reference + midaxillary line (typically), excludes latissimus (lat.) dorsi muscle</td>
<td>sternum-rib junction</td>
</tr>
<tr>
<td>Heart</td>
<td>contour beginning just inferior to the level in which the pulmonary trunk branches into the left and right pulmonary arteries (PA)</td>
<td>location where the heart is no longer apparent on the planning image; the heart blends with the diaphragm and the liver at its inferior aspect</td>
<td>pericardium</td>
<td>excludes descending aorta, esophagus, and vertebral body</td>
<td>pericardium</td>
<td>pericardium</td>
</tr>
<tr>
<td>Lung</td>
<td>pleura</td>
<td>pleura</td>
<td>pleura</td>
<td>pleura</td>
<td>pleura</td>
<td>pleura</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>foramen magnum (or superior-most planning image slice, if foramen magnum not included)</td>
<td>inferior aspect of L3 vertebra (or inferior-most planning image slice, if L3 not included)</td>
<td>as apparent on the planning image</td>
<td>as apparent on the planning image</td>
<td>as apparent on the planning image</td>
<td>as apparent on the planning image</td>
</tr>
</tbody>
</table>

Notes:
(a) Heart: the following structures, if identifiable, are recommended to be excluded from the heart contour: esophagus, great vessels (ascending and descending aorta, inferior vena cava); need not
include pericardial fat, if present; contouring along the pericardium itself, when visible, is appropriate

(b) Lung: the lung volume within the pleural surface, excluding the ribs, mediastinum, and diaphragm, can be auto-contoured (using grayscale-level differences) by most planning systems; the contours shall be verified manually

5.4.6 Dose Prescription

Table 9. Dose descriptions for conventional standard fractionation (PTV_WB EVA); (50 Gy in 25 fractions to the intact breast; additional 10 Gy optional boost to lumpectomy PTV)

<table>
<thead>
<tr>
<th>Target Standard Name</th>
<th>Dose (Gy)</th>
<th>Fraction Size (Gy)</th>
<th># of fractions</th>
<th>Frequency</th>
<th>Dose specification technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV_Lump_EVA</td>
<td>50</td>
<td>2.0</td>
<td>25</td>
<td>Daily</td>
<td>Covering 95% of PTV_Lump_EVA</td>
</tr>
<tr>
<td>PTV_WB_EVA</td>
<td>50</td>
<td>2.0</td>
<td>25</td>
<td>Daily</td>
<td>Covering 95% of PTV_WB_EVA</td>
</tr>
<tr>
<td>PTV_Lump_EVA Boost (Optional)</td>
<td>10</td>
<td>2.0</td>
<td>5</td>
<td>Daily</td>
<td>Covering 95% of PTV_Lump_EVA</td>
</tr>
</tbody>
</table>

Table 10. Dose descriptions for conventional hypofractionation to intact breast only (42.56 Gy in 16 fractions to intact breast or chest wall; additional 10 Gy optional boost to lumpectomy PTV)

<table>
<thead>
<tr>
<th>Target Standard Name</th>
<th>Dose (Gy)</th>
<th>Fraction Size (Gy)</th>
<th># of fractions</th>
<th>Frequency</th>
<th>Dose specification technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV_Lump_EVA</td>
<td>42.56</td>
<td>2.66</td>
<td>16</td>
<td>Daily</td>
<td>Covering 95% of PTV_Lump_EVA</td>
</tr>
<tr>
<td>PTV_WB_EVA</td>
<td>42.56</td>
<td>2.66</td>
<td>16</td>
<td>Daily</td>
<td>Covering 95% of PTV_WB_EVA</td>
</tr>
<tr>
<td>PTV_Lump_EVA boost (Optional)</td>
<td>10</td>
<td>2.54</td>
<td>4</td>
<td>Daily</td>
<td>Covering 95% of PTV_Lump_EVA</td>
</tr>
</tbody>
</table>

Table 11. Dose descriptions for accelerated partial breast irradiation to partial breast only (38.50 Gy in 10 fractions twice daily OR 30 Gy in 5 fractions daily)

<table>
<thead>
<tr>
<th>Target Standard Name</th>
<th>Dose (Gy)</th>
<th>Fraction Size (Gy)</th>
<th># of fractions</th>
<th>Frequency</th>
<th>Dose specification technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV_Lump_EVA (option 1)</td>
<td>38.50</td>
<td>3.85</td>
<td>10</td>
<td>Twice daily</td>
<td>Covering 95% of PTV_Lump_EVA</td>
</tr>
<tr>
<td>PTV_Lump_EVA (option 2)</td>
<td>30</td>
<td>6</td>
<td>5</td>
<td>Daily</td>
<td>Covering 95% of PTV_Lump_EVA</td>
</tr>
</tbody>
</table>

5.4.7 Recommended Compliance Criteria

The compliance criteria listed here are recommended to evaluate plan quality. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. These are intended as guidelines. The Per Protocol and
Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and it is recommended that additional treatment planning optimization be done.

**Normalization of Dose:** The plan is normalized such that 95% of the PTV_WB_EVA or PTV_Lump_EVA volume receives prescription dose of the selected regimen.

**Note:** Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met.

**Target Volume Constraints and Compliance Criteria**

<table>
<thead>
<tr>
<th>Name of Structure</th>
<th>Dosimetric parameter</th>
<th>Per Protocol</th>
<th>Variation Acceptable</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV_Lump_EVA</td>
<td>V95%[%]</td>
<td>&gt;=95%</td>
<td>&gt;=90%</td>
<td>includes boost dose</td>
</tr>
<tr>
<td>PTV_Lump_EVA</td>
<td>V110%[%]</td>
<td>&lt;=5%</td>
<td>&lt;=8%</td>
<td>includes boost dose</td>
</tr>
<tr>
<td>PTV_Lump_EVA</td>
<td>D0.03cc[Gy]</td>
<td>&lt;=115%</td>
<td>&lt;=120%</td>
<td>includes boost dose</td>
</tr>
<tr>
<td>PTV_WB_EVA</td>
<td>V95%[%]</td>
<td>&gt;=95%</td>
<td>&gt;=90%</td>
<td>includes boost dose</td>
</tr>
<tr>
<td>PTV_WB_EVA</td>
<td>V100%[%]</td>
<td>&lt;=30%</td>
<td>&lt;=35%</td>
<td>includes boost dose</td>
</tr>
<tr>
<td>PTV_WB_EVA</td>
<td>D50%[%]</td>
<td>&lt;=108%</td>
<td>&lt;=112%</td>
<td>includes boost dose</td>
</tr>
</tbody>
</table>

Per Protocol range is excluded from Variation Acceptable range.

**Normal Structure Constraints and Compliance Criteria**

Conventional hypofractionation (42.56 Gy in 16 fractions or 40 Gy in 15 fractions for WBI or PBI).

<table>
<thead>
<tr>
<th>Name of Structure</th>
<th>Dosimetric parameter</th>
<th>Per Protocol</th>
<th>Variation Acceptable</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung_L</td>
<td>V16Gy[%]</td>
<td>&lt;=15%</td>
<td>&lt;=20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V8Gy[%]</td>
<td>&lt;=35%</td>
<td>&lt;=40%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V4Gy[%]</td>
<td>&lt;=50%</td>
<td>&lt;=55%</td>
<td></td>
</tr>
<tr>
<td>Lung_R</td>
<td>V4Gy[%]</td>
<td>&lt;=10%</td>
<td>&lt;=15%</td>
<td></td>
</tr>
<tr>
<td>Breast_R</td>
<td>D0.03cc[Gy]</td>
<td>&lt;=2.4 Gy</td>
<td>&lt;=3.4 Gy</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>V16Gy[%]</td>
<td>&lt;=5%</td>
<td>&lt;=10%</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>Mean[Gy]</td>
<td>&lt;=1.6 Gy</td>
<td>&lt;=3.2 Gy</td>
<td></td>
</tr>
<tr>
<td>Spinal_Cord</td>
<td>D0.03cc[Gy]</td>
<td>&lt;=34 Gy</td>
<td>&lt;=39 Gy</td>
<td></td>
</tr>
</tbody>
</table>
Table 14. Example set of constraints and compliance criteria for normal structures using conventional hypofractionation, if right side breast is treated

<table>
<thead>
<tr>
<th>Name of Structure</th>
<th>Dosimetric parameter</th>
<th>Per Protocol</th>
<th>Variation Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung_R</td>
<td>V16Gy[%]</td>
<td>&lt;=15%</td>
<td>&lt;=20%</td>
</tr>
<tr>
<td></td>
<td>V8Gy[%]</td>
<td>&lt;=35%</td>
<td>&lt;=40%</td>
</tr>
<tr>
<td></td>
<td>V4Gy[%]</td>
<td>&lt;=50%</td>
<td>&lt;=55%</td>
</tr>
<tr>
<td>Lung_L</td>
<td>V4Gy[%]</td>
<td>&lt;=10%</td>
<td>&lt;=15%</td>
</tr>
<tr>
<td>Breast_L</td>
<td>D0.03cc[Gy]</td>
<td>&lt;=2.4 Gy</td>
<td>&lt;=3.4 Gy</td>
</tr>
<tr>
<td>Heart</td>
<td>V16Gy[%]</td>
<td>&lt;=0%</td>
<td>&lt;=1%</td>
</tr>
<tr>
<td>Heart</td>
<td>Mean[Gy]</td>
<td>&lt;=0.8Gy</td>
<td>&lt;=1.6 Gy</td>
</tr>
<tr>
<td>Spinal_Cord</td>
<td>D0.03cc[Gy]</td>
<td>&lt;=34 Gy</td>
<td>&lt;=39 Gy</td>
</tr>
</tbody>
</table>

Note: If a boost is included in treatment plan for any whole breast regimen, the compliance criteria should still be met for at least the Variation Acceptable criteria.

Conventional standard fractionation (50 Gy in 25 fractions for WBI):

Table 15. Example set of constraints and compliance criteria for normal structures using conventional standard fractionation, if left side breast is treated

<table>
<thead>
<tr>
<th>Name of Structure</th>
<th>Dosimetric parameter</th>
<th>Per Protocol</th>
<th>Variation Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung_L</td>
<td>V20Gy[%]</td>
<td>&lt;=15%</td>
<td>&lt;=20%</td>
</tr>
<tr>
<td>Lung_L</td>
<td>V10Gy[%]</td>
<td>&lt;=35%</td>
<td>&lt;=40%</td>
</tr>
<tr>
<td>Lung_L</td>
<td>V5Gy[%]</td>
<td>&lt;=50%</td>
<td>&lt;=55%</td>
</tr>
<tr>
<td>Lung_R</td>
<td>V5Gy[%]</td>
<td>&lt;=10%</td>
<td>&lt;=15%</td>
</tr>
<tr>
<td>Breast_R</td>
<td>D0.03cc[Gy]</td>
<td>&lt;=3.1 Gy</td>
<td>&lt;=5 Gy</td>
</tr>
<tr>
<td>Breast_R</td>
<td>D5%[Gy]</td>
<td>&lt;=1.86 Gy</td>
<td>&lt;=3.1 Gy</td>
</tr>
<tr>
<td>Heart</td>
<td>D5%[Gy]</td>
<td>&lt;=20 Gy</td>
<td>&lt;=25 Gy</td>
</tr>
<tr>
<td>Heart</td>
<td>V10Gy[%]</td>
<td>&lt;=30%</td>
<td>&lt;=35%</td>
</tr>
<tr>
<td>Heart</td>
<td>Mean[Gy]</td>
<td>&lt;=2 Gy</td>
<td>&lt;=3 Gy</td>
</tr>
<tr>
<td>Spinal_Cord</td>
<td>D0.03cc[Gy]</td>
<td>&lt;=40 Gy</td>
<td>&lt;=45 Gy</td>
</tr>
</tbody>
</table>

Per Protocol range is excluded from Variation Acceptable range.

Table 16. Example set of constraints and compliance criteria for normal structures using conventional standard fractionation, for WBI if right side breast is treated

<table>
<thead>
<tr>
<th>Name of Structure</th>
<th>Dosimetric parameter</th>
<th>Per Protocol</th>
<th>Variation Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung_R</td>
<td>V20Gy[%]</td>
<td>&lt;=15%</td>
<td>&lt;=20%</td>
</tr>
<tr>
<td>Lung_R</td>
<td>V10Gy[%]</td>
<td>&lt;=35%</td>
<td>&lt;=40%</td>
</tr>
<tr>
<td>Lung_R</td>
<td>V5Gy[%]</td>
<td>&lt;=50%</td>
<td>&lt;=55%</td>
</tr>
<tr>
<td>Lung_L</td>
<td>V5Gy[%]</td>
<td>&lt;=10%</td>
<td>&lt;=15%</td>
</tr>
<tr>
<td>Breast_L</td>
<td>D0.03cc[Gy]</td>
<td>&lt;=3.1 Gy</td>
<td>&lt;=5 Gy</td>
</tr>
<tr>
<td>Breast_L</td>
<td>D5%[Gy]</td>
<td>&lt;=1.86 Gy</td>
<td>&lt;=3.1 Gy</td>
</tr>
<tr>
<td>Heart</td>
<td>D5%[Gy]</td>
<td>&lt;=10 Gy</td>
<td>&lt;=15 Gy</td>
</tr>
<tr>
<td>Heart</td>
<td>V10Gy[%]</td>
<td>&lt;=10%</td>
<td>&lt;=15%</td>
</tr>
<tr>
<td>Heart</td>
<td>Mean[Gy]</td>
<td>&lt;=1 Gy</td>
<td>&lt;=2 Gy</td>
</tr>
<tr>
<td>Spinal_Cord</td>
<td>D0.03cc[Gy]</td>
<td>&lt;=40 Gy</td>
<td>&lt;=45 Gy</td>
</tr>
</tbody>
</table>
Table 17. Example set of constraints and compliance criteria for normal structures using APBI accelerated partial breast irradiation, 3D conformal or IMRT techniques permitted

<table>
<thead>
<tr>
<th>Name of Structure</th>
<th>Dosimetric parameter</th>
<th>Per Protocol</th>
<th>Variation Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung_Ipsi</td>
<td>V11.55Gy[%]</td>
<td>&lt;=15%</td>
<td>&lt;=20%</td>
</tr>
<tr>
<td>Lung_Contra</td>
<td>V1.92Gy[%]</td>
<td>&lt;=15%</td>
<td>&lt;=20%</td>
</tr>
<tr>
<td>Breast_Ipsi</td>
<td>V19.25Gy[%]</td>
<td>&lt;=50%</td>
<td>&lt;=60%</td>
</tr>
<tr>
<td></td>
<td>V38.5Gy[%]</td>
<td>&lt;=30%</td>
<td>&lt;=35%</td>
</tr>
<tr>
<td>Breast_Contra</td>
<td>D0.03cc[Gy]</td>
<td>&lt;=1.15 [Gy]</td>
<td>&lt;=1.92 [Gy]</td>
</tr>
<tr>
<td>Heart (right sided tumor)</td>
<td>V1.92Gy[%]</td>
<td>&lt;=5%</td>
<td>-</td>
</tr>
<tr>
<td>Heart (left sided tumor)</td>
<td>V1.92Gy[%]</td>
<td>&lt;=40%</td>
<td>-</td>
</tr>
<tr>
<td>Heart (left sided)</td>
<td>Mean [Gy]</td>
<td>&lt; 0.8 Gy</td>
<td>&lt; 1.5 Gy</td>
</tr>
<tr>
<td>Spinal_Cord</td>
<td>D0.03cc[Gy]</td>
<td>&lt;=30 [Gy]</td>
<td>&lt;=34 [Gy]</td>
</tr>
</tbody>
</table>

5.4.8 Treatment Planning Priorities and Instructions

Critical Structure and Target prioritization is recommended as below:
1. Heart
2. CTV
3. Ipsilateral lung
4. PTV
5. Breast
6. Contralateral lung
7. Contralateral breast

For all planning techniques, treatment beam trajectories entering through regions truncated by the image FOV are not permitted. If low-density or high-density hardening artifacts appear in the image within regions known to be of uniform density, metal artifact reduction or density-override contours may be used. Attenuation from treatment couch, e.g., when patient is treated prone, should be accounted for by modelling the couch components with assigned electron densities and correct couch top position.

5.4.9 Patient Specific QA

Any patient-specific QA that needs to be acquired should follow institutional guidelines.

For IMRT or VMAT plans, patient specific QA is highly recommended. Any patient-specific QA performed should follow institutional guidelines. The recommended patient specific QA criterion is for 90% of the comparison points to pass a ±3%/3mm Gamma Index analysis.

For forward-planned EBRT delivery, verification of the MU calculation for each field within the TPS shall be performed prior to administration of the first fraction. The independent MU calculation should be consistent with that of TPS within the tolerance per institution guideline.

For inverse-planned EBRT delivery, a direct measurement of the dose distribution from the designated treatment system shall be performed prior to delivery of the first fraction.

5.4.10 Daily Treatment Localization/IGRT

Verification Simulation Required Prior to the First Fraction of Treatment
Prior to delivery of the first fraction, the position of the patient relative to the radiation source shall be verified through either planar radiographs or volumetric images. Delivering the first fraction on the same day as the above pre-treatment verification measurements is optional.

Verification during Subsequent Fractions

For treatments prescribed for five or more consecutive-daily fractions, imaging for position verification shall be performed prior to fraction delivery once at least every five fractions.

Management of Radiation Dose to the Patient from IGRT

NRG Oncology is concerned about the estimated irradiation doses given from IGRT and is committed to limiting the imaging dose when IGRT is used in any of its protocols. This can be accomplished by avoiding the use of this technology to make small changes in patient positioning that are within the stated PTV margins. The imaging dose to the patient may become significant if repeated studies are done for patients with severe set up problems (e.g., requiring frequent corrections that are larger than the PTV margins). It is recommended that patients demonstrating severe set up problems during the first week of treatment be re-planned and treated with larger margins.

If possible, verification imaging dose shall be calculated or estimated within the TPS. An action level for excess dose due to unplanned verification imaging, as well as the measures to take if the action level is reached or exceeded, shall be established by the institution and subject to approval by the protocol.

5.4.11 Modality Reviews: RT Quality Assurance Reviews

Each case assigned to ARM1 radiation will undergo quality assurance reviews. Principal Investigators, Eleanor Harris, MD and Julia White, MD will perform ongoing remote RT Quality Assurance Review after cases enrolled have been received at IROC Philadelphia-RT. NRG Oncology Headquarters approved designee will perform an RT Quality Assurance Review after IROC Philadelphia-RT has received complete data in TRIAD. The RT reviews will be ongoing and performed remotely. The final cases will be reviewed within 6 months after this study has reached the target accrual or as soon as IROC-Philadelphia RT has received complete data in TRIAD for all cases enrolled, whichever occurs first. The scoring mechanism is: Per Protocol, Variation Acceptable, and Unacceptable Deviation.

The secondary aim is intended to evaluate the feasibility of implementation of AI in radiotherapy quality assurance. Radiotherapy quality assurance is crucial and could potentially affect clinical trial outcome (Ohri 2014). Due to the large sample size and well-established consensus on the definition of the structures, we are in a good position to apply the AI models we built as part of the quality assurance process.

Machine learning and artificial intelligence have been implemented in the segmentation of structures for radiation therapy (Liesbeth 2020). The performance for some of the structures has been reported to be satisfactory, with volume overlap for OARs in the thoracic region around 90% (Men 2020; Yang 2018), within the uncertainties of inter-observer variations, with reported volume overlap around 80% for these thoracic OARs (Li 2009). The deep learning algorithm for automated contouring has been implemented successfully not only in published research papers, as included in the references specifically for breast disease site (Choi 2020; Schreier 2019), but also in FDA approved commercial packages, such as MiMsoftware, Mirada, etc. It is well in its application phase. The deep learning models we built from the thorax datasets included submissions from multiple institutions of various imaging configurations and have excellent...
performance (Men 2020). We expect the models will accommodate the variations from the image sets from this protocol, as we have image pre-processing as part of the process. It is also our plan to make adjustments to the models as we evaluate the performance during the conduct of the trial. We will use these models to perform structure review for the first submitted 50 cases, along with the reviewers specified above. Review strategy, machine learning models will be adjusted and adapted from the continuous analysis. We will have parallel reviews from AI and experts until we have reached equivalency, beyond which experts will spot check AI reviews.

**Radiation Therapy Reviews**

The contours are scored as per protocol, variation acceptable, deviation unacceptable, and not evaluable. Cases that are not evaluable will be considered as such regardless of the reviewer. Reviewer scores from the AI algorithm will be compared with those from the radiation oncologist. It should be noted that there will be multiple radiation oncologists who will allow the AI algorithm not to be dependent on a single reviewer but rather the contours, as expressed in Section 5.4.11. The statistical analysis strategy described in detail below will be used to assess the inter-rater reliability between the AI algorithm and radiation oncologists. If the threshold from the statistical analysis is not met in the initial group of patients, then the AI algorithm will be modified appropriately to be assessed and compared in another cohort of patients. This process will continue until we have reached the statistical performance threshold. At this point, only the AI algorithm will be used to perform the QA of the RT structures.

The procedure includes the following processes: for every 50 cases, we will evaluate the volume overlap and distance of agreement between AI-generated contours and those submitted. Quality scores are assigned with the thresholds developed from prior cases (Men 2020). These scores are compared with those from reviewers. Discrepancies are resolved with discussions with reviewers and updating the AI model when appropriate. If the image set is to be included in the updated model, we will perform the pre-processing of the image set and train the CNN model (Kuo 2020) with the added image sets. There may be a need to fine tune the parameters of the models for better performance. The updated model will be validated with image/contour sets that were processed before the update as part of the quality assurance process. Software scripts for evaluation of image quality parameters to identify outliers that might affect AI model performance will be implemented as part of the preprocessing before utilizing AI models.

**Power Calculations:**

Radiation Therapy Reviews

An AI algorithm will be developed to perform QA on RT structures. Because there will be multiple reviewers and no “gold standard”, Fleiss’s $\kappa$ statistic along with concordance and discordance frequencies will be computed to assess the inter-rate reliability between the AI algorithm and radiation oncologists. Since a relatively high level of agreement between the scores from the AI algorithm and radiation oncologists is expected, it is assumed that $\kappa=0.70$ under the null hypothesis. The threshold for agreement will be set very high, at $\kappa \geq 0.95$, with the goal of the AI algorithm being able to perform reviews independently. Other trials tend to see a high proportion of cases scored as per protocol with very few, if any, scored as not per protocol. Thus, the marginal probabilities assumed are listed below.
Score Marginal probabilities
Per protocol 0.65
Acceptable variation 0.25
Unacceptable variation 0.10

Using a one-sided type I error of 0.025, a sample of 82 evaluable patients will provide 95% statistical power. Evaluable patients will be considered randomized patients who received RT with RT structures available for review.

5.5 General Concomitant Medications and Supportive Care Guidelines

5.5.1 Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the treating physician(s) within the parameters of the protocol and documented on each site’s source documents as concomitant medication. Analgesic medication to avoid general discomfort during simulation and treatment as well as to manage radiation therapy and/or endocrine therapy toxicities is recommended when appropriate. Topical medium potency steroids to treat acute dermatitis is recommended to treat pruritus as necessary. Similarly, medical therapy to support symptom management related to endocrine treatment is recommended as necessary. Oral, transdermal, or subdermal estrogen replacement therapy for management of postmenopausal symptoms is not permitted (including all estrogen only and estrogen-progesterone formulas). Vaginal estrogens are acceptable for management of vaginal symptoms. Bone-directed therapy, bisphosphonates and denosumab are allowed.

5.5.2 Participation in Other Trials

Patients are not permitted to participate in other therapeutic trials. However, trials that do not add experimental agents are allowed (e.g. imaging trials, quality of life, etc.). If a BR007 patient is considering participation in a supportive therapy trial, contact the NRG Oncology Clinical Coordinating Department.

5.6 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment should continue as specified in the above treatment modality sections until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
- Pregnancy
  - All women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
  - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a female patient or the partner of a male patient participating in the study.
- Termination of the study by sponsor

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be reported in the Case Report Form.
6.0 TREATMENT MODIFICATIONS/MANAGEMENT

- The CTCAE v5.0 must be used to grade the severity of AEs. Refer to http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
7.0 ADVERSE EVENT REPORTING REQUIREMENTS

7.1 Study Agents

The commercial agents in NRG-BR007 are endocrine therapy: tamoxifen, anastrozole, exemestane, and letrozole, with or without ovarian function suppression per standard practice (LHRH agonist/antagonists [e.g., Lupron™ and Zoladex™]).

7.2 Adverse Events and Serious Adverse Events

7.2.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7.2.2 Definition of an Adverse Event (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).

For multi-modality trials, adverse event reporting encompasses all aspects of study treatment including radiation therapy, surgery, device, and drug.

7.3 Adverse Events for Commercial Agents

Refer to the current FDA-approved package insert or current Health Canada-approved product monograph for detailed pharmacologic and safety information for the endocrine therapy used.

7.4 Adverse Events for Radiation Therapy

- **Short Term**
  Common local reactions include skin erythema, hyperpigmentation, pruritus, desquamation, breast edema, breast tenderness, and myositis. Fatigue is an anticipated systemic reaction to radiation treatment.

- **Long Term**
  Long term effects possibly include radiation pneumonitis, rib fractures, and for left-sided lesions there could be cardiac complications.
7.5 Expedited Reporting of Adverse Events

All serious adverse events that meet expedited reporting criteria defined in Table 18 will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via RAVE-CTEP-AERS Integration.

Refer to Section 13.4 for important operational details/information about RAVE-CTEP-AERS Integration and how to obtain the Expedited Safety Reporting Rules Evaluation User Guide.

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-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 the NRG Oncology Statistics and Data Management Center by telephone at 412-624-2666. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.5.1 Expedited Reporting Methods

• **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 complete report within 5 days.

• **Supporting source documentation** is requested by NRG Oncology as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page. Contact the NRG Oncology Statistics and Data Management Center at number 412-624-2666 for source documentation assistance.

• A serious adverse event that meets expedited reporting criteria as outlined in the AE Reporting Table but is assessed by the CTEP-AERS as “an action not recommended” must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the “NOT recommended” assessment. The CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.5.2 Expedited Reporting Requirements

Expedited reporting requirements begin with the administration of the first radiation therapy dose. Expedited reporting requirements for all patients are provided in Table 18.
Table 18. Expedited reporting requirements for adverse events that occur within 30 days of the last dose of radiation therapy ¹

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 Timeframes</th>
<th>Grade 2 Timeframes</th>
<th>Grade 3 Timeframes</th>
<th>Grade 4 &amp; 5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting in Hospitalization ≥ 24 hrs</td>
<td>Not required</td>
<td></td>
<td>10 Calendar Days</td>
<td>24-Hour, 5 Calendar Days</td>
</tr>
<tr>
<td>Not resulting in Hospitalization ≥ 24 hrs</td>
<td>Not required</td>
<td></td>
<td>10 Calendar Days</td>
<td></td>
</tr>
</tbody>
</table>

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.

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

**Expedited 24-hour notification followed by complete report with 5 calendar days for:**
- All Grade 4 and Grade 5 AEs

**Expedited 10 calendar day reports for:**
- Grade 3 adverse events

Effective Date: May 5, 2011
7.5.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.5.4 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 during or subsequent to treatment with an agent under an NCI IND/IDE to be reported via CTEP-AERS. In addition, secondary malignancies following radiation therapy must 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 BR007 Follow-up Folder in Medidata Rave. Supporting documentation should be uploaded into the relevant form in the Follow-up folder in Medidata Rave using available upload fields within those forms. Please upload each document into a different upload field, as any later uploads into a given field erases the document that exists there.

7.5.5 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 within the BR007 Follow-up Folder in Medidata Rave.

7.5.6 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via CTEP-AERS. In addition, the Pregnancy Information Form included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient from the time of consent to 30 days after the last dose of radiation therapy must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the “NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs” (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

7.6 Routine Reporting of Adverse Events

7.6.1 Reporting Routine Adverse Events Through Medidata Rave

- Reporting of routine adverse events is done through Medidata Rave (see Section 13.2).
- All ≥ grade 2 adverse events that occurred during radiation therapy or during the 30 days following the last dose of radiation therapy must be reported in Medidata Rave, regardless of whether these adverse events are expected or unexpected.
• Supporting documentation for each AE reported on the BR007 Adverse Event forms through Medidata Rave must be maintained in the patient's research record. When submission of supporting documentation to the NRG Oncology Statistics and Data Management Center is required, remove patient names and identifiers such as social security number, address, telephone number, etc., from reports and supporting documentation.

7.6.2 Schedule for Reporting Routine Adverse Events

Adverse events forms are to be submitted through Medidata Rave, even if no AEs were experienced by the patient, according to the following schedule:

• Submit the BR007 Adverse Event Report Form at the end of radiation therapy for Arm 1 or at 3 months after randomization for Arm 2.
• Submit the BR007 Adverse Event Report Form 30 days after the end of radiation therapy (not required for Arm 2 patients).
• Submit the BR007 Adverse Event Report Form 6, 12, 18, and 24 months from randomization and every 12 months for Years 3-10 from randomization.

7.7 Reporting Breast Cancer Recurrence and Second Primary Cancer

Report breast cancer recurrence and second primary cancer (a malignancy which is unrelated to the treatment of a prior malignancy and which is not a metastasis from the initial malignancy) within the BR007 Follow-up folder in Medidata Rave. Supporting documentation should be uploaded into the relevant form in the Follow-up folder in Medidata Rave using available upload fields within those forms. Please upload each document into a different upload field, as any later uploads into a given field erases the document that exists here. (See Section 7.5.4 for reporting instructions for secondary malignancies.)

7.8 Reporting Late Cardiac Toxicity Information

Report late cardiac toxicity information (≥ grade 2 cardiac toxicity), annually through Year 5 within the BR007 Follow-up folder in Medidata Rave. Supporting documentation should be uploaded into the relevant form in the Follow-up folder in Medidata Rave using available upload fields within those forms. Please upload each document into a different upload field, as any later uploads into a given field erases the document that exists here.
8.0 REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES

8.1 Investigator and Research Associate Registration with CTEP

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

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

<table>
<thead>
<tr>
<th>Documentation Required</th>
<th>IVR</th>
<th>NPIVR</th>
<th>AP</th>
<th>A</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Form 1572</td>
<td>✅</td>
<td>✅</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial Disclosure Form</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCI Biosketch (education, training, employment, license, and certification)</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCP training</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agent Shipment Form (if applicable)</td>
<td>✅</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV (optional)</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:
• An addition to a site roster
• Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
• Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
• Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

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

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

8.2 Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

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

8.2.1 IRB Approval

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

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB’s approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURregPref@ctsu.comcg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

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

• Local IRB documentation;
• IRB-signed CTSU IRB Certification Form; and/or

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:
• Holds an Active CTEP status;
• Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster;
• If using NCI CIRB, rostered on the NCI CIRB Signatory record;
• Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
• Holds the appropriate CTEP registration type for the protocol.

8.2.2 Additional Requirements

Additional requirements to obtain an approved site registration status include:

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

8.2.3 Protocol-Specific Requirements for NRG-BR007 Site Registration

Radiation Requirements

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

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

To complete protocol-specific credentialing the RTI provider or enrolling site should follow instructions in protocol Section 8.2.4 to submit documentation or other materials to the designated IROC Quality Assurance (QA) center. Upon the IROC QA center approving the RTI provider for the study modality, IROC will send a credentialing email to the provider. The provider will then need to upload to the CTSU Regulatory Submission Portal so that the Regulatory Support System (RSS) can be updated to show that the provider complies with the protocol-specific requirement.

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist.
8.2.4 RT Specific Pre-Registration Requirements

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, IROC Houston will notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study. The credentialing notification document (email) must be uploaded by the site to the CTSU Regulatory Submission Portal for RSS to be updated.

<table>
<thead>
<tr>
<th>RT Credentialing Requirements</th>
<th>Web Link for Credentialing Procedures and Instructions</th>
<th>IMRT</th>
<th>Key Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Credentialing Status Inquiry Form</td>
<td></td>
<td>x</td>
<td>To determine whether your institution needs to complete any further credentialing requirements, please complete the “Credentialing Status Inquiry Form” found under credentialing on the IROC Houston QA Center website (<a href="http://irochouston.mdanderson.org">http://irochouston.mdanderson.org</a>)</td>
</tr>
<tr>
<td>Facility Questionnaire</td>
<td></td>
<td>x</td>
<td>The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ go to <a href="http://irochouston.mdanderson.org/questionnaires/">http://irochouston.mdanderson.org/questionnaires/</a></td>
</tr>
<tr>
<td>Phantom Irradiation</td>
<td></td>
<td>x</td>
<td>An IMRT Head &amp; Neck phantom study provided by the IROC Houston QA Center must be successfully completed (if the institution has not previously met this credentialing requirement). Flattening-filter-free (FFF) photon beam delivery and Tomotherapy treatment delivery modalities must be credentialed individually. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (<a href="http://irochouston.mdanderson.org">http://irochouston.mdanderson.org</a>).</td>
</tr>
</tbody>
</table>

Credentialing Notification Issued to:

Institution

Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and NRG Headquarters that all desired credentialing requirements have been met.
8.2.5 **Downloading Site Registration Documents**

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

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select NRG Oncology, and protocol number (NRG-BR007);
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

8.2.6 **Submitting Regulatory Documents**

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

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

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

8.2.7 **Checking Site's Registration Status**

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

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

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

8.3 **Non-English Speaking Canadian 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. 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 organization/letterhead stationery that includes the professional title, credentials, and signature of the translator.
8.4 **Patient Enrollment**

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

Requirements for OPEN access:

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

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

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

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

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

Access OPEN at [https://open.ctsu.org](https://open.ctsu.org) or from the OPEN link on the CTSU members’ website. Further instructional information is in the OPEN section of the CTSU website at [https://www.ctsu.org](https://www.ctsu.org) or [https://open.ctsu.org](https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

8.5 **Digital Radiation Therapy Data Submission Using Transfer of Images and Data (TRIAD)**

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

TRIAD Access Requirements:

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

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.
TRIAD Installation:
To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.
This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.
For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

8.6 Reimbursement

To receive site reimbursement for biospecimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Refer to the protocol-specific funding page on the CTSU members’ website for additional information (Protocol NRG-BR007 > Funding Information.). Timely entry of completion dates is recommended as this will trigger site reimbursement.

8.7 Investigator-Initiated Discontinuation of Study Therapy

In addition to the conditions outlined in the protocol, the investigator may require a patient to discontinue study therapy if one of the following occurs:

- the patient develops a serious side effect that cannot be tolerated or that cannot be controlled with other medications,
- the patient's health gets worse,
- the patient is unable to meet the study requirements, or
- new information about the study therapy or other treatments for breast cancer becomes available.

If study therapy is stopped, study data, other materials, and the tumor samples (at the time of disease progression) should be submitted according to the study schedule unless the patient withdraws from the study (see Section 8.9).

8.8 Patient-Initiated Discontinuation of Study Therapy

Even after a patient agrees to take part in this study, the patient may stop study therapy or withdraw from the study at any time. If study therapy is stopped but the patient still allows the investigator to submit information, study data, other materials, and the tumor samples (at the time of disease progression) should be submitted according to the study schedule.

8.9 Patient-Initiated Consent Withdrawal from the Study

If a patient chooses to have no further interaction regarding the study (i.e., allow no future follow-up data to be submitted to NRG Oncology), the consent withdrawal form is to be completed via the Add-Event function in Medidata Rave.
9.0 **DRUG INFORMATION**

Tamoxifen, anastrozole, exemestane, letrozole, and LHRH agonist/antagonists (e.g., Lupron® and Zoladex®) are obtained by the investigator from commercial supply.

9.1 **Tamoxifen (NSC #180973)**

Sites must refer to the package insert for detailed pharmacologic and safety information.

9.1.1 **Adverse Events**

Refer to the tamoxifen package insert or monograph.

9.1.2 **Availability/Supply**

Please see Section 5.3 for administration instructions. Refer to the current FDA-approved package inserts or current Health Canada-approved product monographs provided with the drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

9.2 **Anastrozole (NSC #719344)**

Sites must refer to the package insert for detailed pharmacologic and safety information.

9.2.1 **Adverse Events**

Refer to the anastrozole package insert or monograph.

9.2.2 **Availability/Supply**

Please see Section 5.3 for administration instructions. Refer to the current FDA-approved package inserts or current Health Canada-approved product monographs provided with the drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

9.3 **Exemestane (NSC #713563)**

Sites must refer to the package insert for detailed pharmacologic and safety information.

9.3.1 **Adverse Events**

Refer to the exemestane package insert or monograph.

9.3.2 **Availability/Supply**

Please see Section 5.3 for administration instructions. Refer to the current FDA-approved package inserts or current Health Canada-approved product monographs provided with the drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.
9.4 **Letrozole (NSC #719345)**
Sites must refer to the package insert for detailed pharmacologic and safety information.

9.4.1 **Adverse Events**
Refer to the letrozole package insert or monograph.

9.4.2 **Availability/Supply**
Please see Section 5.3 for administration instructions. Refer to the current FDA-approved package inserts or current Health Canada-approved product monographs provided with the drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

9.5 **Goserelin acetate (Zoladex®) (NSC #606864)**
Sites must refer to the package insert for detailed pharmacologic and safety information.

9.5.1 **Adverse Events**
Refer to the package insert or monograph.

9.5.2 **Availability/Supply**
Please see Section 5.3 for administration instructions. Refer to the current FDA-approved package inserts or current Health Canada-approved product monographs provided with the drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

9.6 **Leuprolide acetate (Lupron®) (NSC #377526)**
Sites must refer to the package insert for detailed pharmacologic and safety information.

9.6.1 **Adverse Events**
Refer to the package insert or monograph.

9.6.2 **Availability/Supply**
Please see Section 5.3 for administration instructions. Refer to the current FDA-approved package inserts or current Health Canada-approved product monographs provided with the drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

9.7 **Triptorelin pamoate (NSC #724666)**
Sites must refer to the package insert for detailed pharmacologic and safety information.

9.7.1 **Adverse Events**
Refer to the package insert or monograph.

9.7.2 **Availability/Supply**
Please see Section 5.3 for administration instructions. Refer to the current FDA-approved package inserts or current Health Canada-approved product monographs provided with the drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.
10.0 PATHOLOGY/BIOSPECIMEN

10.1 Overview of Tumor and Blood Specimen Submissions

Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient’s specimens as specified per protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.

See detailed specimen collection/processing/shipping instructions in the NRG-BR007 Pathology and Correlative Science Instructions.

This study will include collection of biospecimens for future analyses. An amendment for any correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines or via the Navigator portal after the trial has been reported. Amendments to the protocol and/or proposals for use of banked tissue or blood samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

Table 19. Optional sample requirements

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Collection Time Points</th>
<th>Shipping</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFPE Block from primary breast tumor</td>
<td>Baseline (submit within 90 days after randomization)</td>
<td>NRG Oncology Biospecimen Bank-Pittsburgh Pittsburgh, PA 15212</td>
</tr>
<tr>
<td>Blood specimens:</td>
<td>• Baseline for both arms</td>
<td>Baylor College of Medicine Breast Center Houston, TX 77030</td>
</tr>
<tr>
<td></td>
<td>• End of radiation for Arm 1 or 3 months after randomization for Arm 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• After randomization for both arms at:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 12 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 36 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 48 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 60 months</td>
<td></td>
</tr>
</tbody>
</table>

For tissue questions, contact:
NRG Oncology Biospecimen Bank - Pittsburgh
1307 Federal Street, Suite 303
Pittsburgh, PA 15212
Phone: 412-697-6611
E-mail: nrgbiobankpgh@nrgoncology.org

For blood specimen questions, contact:
Baylor College of Medicine Breast Center
NRG Oncology Serum Bank
Room N1111
One Baylor Plaza
Houston, TX 77030
Phone: 713-798-1647

Note: Refer to the NRG-BR007 Pathology and Correlative Science Instructions for tumor and blood sample collection and submission instructions.
10.2 Oncotype DX Recurrence Score testing for patients with a \textit{T1a tumor (≤ 0.5 cm in size)}

Patients with a \textit{T1a tumor (≤ 0.5 cm in size)} who do not have an Oncotype DX Recurrence Score must have a tissue sample sent to Genomic Health for a Recurrence Score to determine eligibility. Central testing of Oncotype DX Recurrence Score will be performed by Genomic Health and Genomic Health will cover the cost of the test. The results will be provided to the ordering physician/institution. When a Recurrence Score result of \( \leq 18 \) is received on central testing for patients with a \textit{T1a tumor (≤ 0.5 cm in size)}, and they meet all other study requirements, the patient should be randomized.

Refer to the NRG-BR007 Pathology and Correlative Science Instructions for ordering the Oncotype DX Recurrence test.

10.3 Use of Specimens

The tumor samples and blood collected in this study will be banked for future studies that will be described in a future amendment.

An amendment or proposal for any additional correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of biological samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

The procured specimens, including DNA samples derived from them, will not be used for hereditary genetic studies involving genes conferring susceptibility to cancer or other diseases unless additional consent is obtained from the patient or an anonymization process is used. Results of the correlative science studies will not be reported to the patient or the patient's physician and will not have any bearing on the patient's treatment.
11.0 **SPECIAL STUDIES (NON-TISSUE)**

11.1 **Health-Related Quality of Life and Patient-Reported Outcomes Background**

11.1.1 **Health-Related Quality of Life (HRQOL) Considerations and Selection of Key Constructs for Measurement**

The impact of omitting radiotherapy on HRQOL after lumpectomy is a key question in this trial. Patient-reported outcomes (PROs) are needed to fill in the critical gap in evidence that exists to guide patients and clinicians about accepting breast conservation with surgery alone without radiotherapy in the study group of stage I hormone sensitive breast cancer identified as “low risk” by RS. Cohort studies and clinical trials conducted outside the United States, where culture and expectations differ, cannot provide the information that is necessary to optimize the impact of this trial question (omission of RT) on clinical practice. Studies conducted with historical radiotherapy techniques not reflecting the current common practices of using hypofractionated whole breast radiotherapy and partial breast irradiation are insufficient to inform patient decisions in the modern era in the United States. Therefore, the HRQOL component of this trial is essential.

Prior research has identified several key constructs that merit evaluation when considering the impact of omitting RT on patient HRQOL. One key area for measurement is breast pain. The long-term follow-up of the randomized Swedish SWEBCG91-RT trial (Lundstedt 2010) suggested durable differences in pain experienced by women randomized to RT (which in that trial involved tangential opposed fields of 4-6 MV photons, 48-54 Gy in 24-27 fractions, administered to the remaining breast parenchyma) (Killander 2016). Specifically, 10-17 years after treatment, pain in the breast or in the skin in that trial was reported to occur "occasionally" by 38.1% of survivors having undergone RT and surgery versus 24.0% of those with surgery alone (absolute difference 14.1%; p=0.004) and at least once a week by 10.3% of the RT group versus 1.7% (absolute difference 8.6%; p=0.001). In the U.S. CALGB 9343 randomized trial, radiotherapy involved tangential fields to the whole breast (dose of 45 Gy in 25 fractions), followed by a boost (up to 14 Gy in 7 fractions), physician-reported breast pain was higher in the irradiated group during the first year only. Patient-reported breast pain was higher for all four years of follow-up (Hughes 2004). In the Canadian OCOG randomized trial, cobalt-60 was used to administer 40 Gy in 16 fractions to the whole breast with parallel, opposed tangents that were partially wedged, followed by a boost of 12.5 Gy in 5 daily fractions. RT was associated with being troubled by breast pain, with the difference most pronounced at 6 months after randomization (33% of patients in the radiation group versus 20% in the control, \( P = 0.0002 \)). By two years, the difference had decreased, and 15% of patients in both groups reported breast pain (Whelan 2000). Differences in chronic pain have also been suggested by studies from Denmark (Tasmuth 1995, Tasmuth 1997, Peuckmann 2009).

The potential impact of omission of radiotherapy on patients’ worry about recurrence is another important issue in need of evaluation, especially among patients with biologically favorable early-stage disease included in this trial. In prior work led by James Hayman, fear of a local recurrence and an actual local recurrence leading to mastectomy had such a negative impact on quality of life that patients were willing to accept the risks and inconvenience of RT to avoid those outcomes in the setting of invasive breast cancer (Hayman 1997). In a subsequent time-trade off study regarding the use of RT after breast conserving surgery (BCS), Hayman et al. examined this same question in DCIS patients, specifically because there is no survival benefit from RT in this setting (Hayman 2005). Because there is no expected difference in survival in the population selected to participate in the current trial, the prior work in the setting of DCIS is relevant here. Hayman’s work concluded that the major benefit associated with adding RT to
BCS in this setting is the ability to reduce invasive recurrences (Hayman 2005). Further information about the patient experience after treatment of breast cancer is available from a series of studies conducted by Steven Katz and his team, including HRQOL study co-chair Reshma Jagsi, examining several thousand patients with DCIS and invasive breast cancer recruited from the Los Angeles and Detroit Surveillance, Epidemiology and End Results (SEER) registries. In an analysis that examined worry about recurrence in this patient sample (Janz 2011), the authors focused on worry about the cancer returning to the same breast, occurring in the other breast, or spreading to other parts of the body. Factors significantly associated with greater worry were race/ethnicity, younger age, being employed, more pain and fatigue, and RT. Latinas were at greatest risk of worry followed by white women and African American women in this sample (Janz 2011). Of note, stage of disease (DCIS vs. invasive) did not influence worry about recurrence. In recent years, trends in local treatment for breast cancer demonstrate that women select overtreatment with contralateral prophylactic mastectomy in addition to mastectomy for their low risk stage 1 breast cancer for, “peace of mind” (Rosenberg 2013, Hawley 2017). This underscores both the availability of measurement tools and the importance of understanding patients’ fears and worries in order to be successful in designing strategies to conquer overtreatment with RT.

Other key constructs for measurement in this setting relate to global quality of life and the additional toxicities known to be associated with RT. These include impact on breast cosmesis, fatigue, breast and skin symptoms, and endocrine therapy adherence and side effects. The British PRIME randomized trial examining omission of RT had quality of life as the primary endpoint (Williams 2011). Although the hypothesized improvement in overall quality of life with the omission of RT was not detected, certain differences did emerge that were particularly apparent shortly after the time of completion of RT, including increased breast symptoms and greater self-reported fatigue in the radiation treatment group, but lower levels of insomnia and endocrine side effects. That trial reported statistically significant differences in breast symptoms that persisted for up to 5 years after RT [mean difference, RT was 5.27 units greater than no RT, 95% confidence interval (CI) of 1.46 to 9.07], with similar, though non-significant, trends in insomnia. Moreover, other research has suggested that differences in cosmesis or patient-reported measures of fatigue and role functioning can be detected even when comparing two different radiation techniques or fractionation schedules, suggesting that comparing these outcomes with and without RT altogether is important (Shaitelman 2015, Jagsi 2015, Ganz 2019, Whelan 2019).

11.1.2 Adherence to Adjuvant Endocrine Therapy (ET)

Adherence to adjuvant ET is challenging for patients with breast cancer, which is largely related to the high frequency and severity of symptoms associated with treatment, such as vasomotor symptoms, musculoskeletal complaints, and vaginal symptoms (Ganz 2016, Wagner 2018, Brauer 2016). Completion of 5 years of ET is a primary recommendation in the setting of early stage hormone sensitive breast cancer and will be recommended to all participants in this trial. We know from the literature (Hershman 2010, Hershman 2011, Hershman 2015, Hershman 2016) and even from NSABP/NRG clinical trials, that only 50-65% of women complete this course of therapy. A potential concern in this trial is that women who will be receiving the standard therapy with radiation will have less motivation to continue on with ET if side effects are intolerable, in comparison to the experimental arm where no RT is received. On the other hand, non-adherence in either group could compromise the primary outcomes being measured in this trial. Due to these concerns, we will collect data on patient reported endocrine symptoms, clinician and patient reported intent and actual continuation of prescribed ET, and assess adherence behavior with a standardized question (Voils 2019).
**11.1.3 Assessment Approach, Considerations, and Questionnaires**

*Table 20* lists the key PRO instruments that will be used on the HRQOL portion of the proposed randomized trial. The primary outcome of pain will be measured by Stanton's Breast Cancer Treatment Outcome Scale (BCTOS) ([Stanton 2001, Krishnan 2001](#)). Breast cancer fear of recurrence will be measured by the Janz/Katz worry questionnaire described earlier ([Janz 2011](#)). All the PRO instruments have excellent psychometric characteristics and have been used in the target populations in other observational or randomized trials. In addition, we will be collecting other information by self-report that includes demographic characteristics (age, ethnicity, marital status, education, employment, income, living situation), other chronic health conditions, global rating of appearance of breast and satisfaction with results of breast cancer treatment.

**Table 20. Proposed Key PRO Instruments**

<table>
<thead>
<tr>
<th>Outcome of Interest</th>
<th>Instrument</th>
<th>Number of items</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcomes:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Pain</td>
<td>BCTOS breast pain (<a href="#">Stanton 2001, Krishnan 2001</a>)</td>
<td>3</td>
</tr>
<tr>
<td>Breast Cancer Fear of Recurrence</td>
<td>Breast cancer worry (<a href="#">Janz 2011</a>)</td>
<td>3</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Quality of Life</td>
<td>PROMIS Global (<a href="#">PROMIS manual</a>)</td>
<td>10</td>
</tr>
<tr>
<td>Breast related functional status</td>
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<tr>
<td>Cosmesis</td>
<td>BCTOS (<a href="#">Stanton 2001, Krishnan 2001</a>); Global Cosmesis Score (<a href="#">White 2019</a>)</td>
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<tr>
<td>Fatigue</td>
<td>PROMIS-Fatigue (<a href="#">Jensen 2017, Jensen 2017</a>)</td>
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<tr>
<td>Breast cancer treatment symptoms</td>
<td>B39 breast symptom checklist (<a href="#">Ganz 2019</a>)</td>
<td>13</td>
</tr>
<tr>
<td>Distress related to cancer recurrence</td>
<td>Quality of life after cancer (<a href="#">Avis 2005</a>)</td>
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<tr>
<td>Adherence questionnaire</td>
<td>Extent of Nonadherence (<a href="#">Voils 2019</a>)</td>
<td>3 on adherence plus selected items for reasons</td>
</tr>
</tbody>
</table>

**11.2 Aims and Hypotheses**

Primary Hypotheses:
1) Patients in the omission of radiation arm will have less pain at 3 years.
2) Patients in the omission of radiation arm will have greater worry about recurrence at 3 years.
Secondary hypotheses:
1) Patients in the omission of radiation arm will report better cosmesis at 3 years.
2) Patients in the omission of radiation arm will have better breast-related functional status at 3 years.
3) Patients in the omission of radiation arm will have less fatigue at 6 months.
4) Patients in the omission of radiation arm will have less breast and skin symptoms at 6 months.
5) Patients in the omission of radiation arm will have greater adherence to endocrine therapy at 5 years.
6) Patients in the omission of radiation arm will have non-inferior global quality of life at 3 years compared to patients receiving breast conservation, breast radiation, and endocrine therapy.

Our primary study hypotheses focus on PRO outcomes at 3 years, but we will also capture the entire trajectory of the patient experience throughout 5 years of HRQOL follow-up. This will provide greater descriptive detail for future patients regarding any early and/or late differences with the omission of RT and will help with the interpretation of the trial results. Several of the QoL measures may meaningfully evolve and demonstrate differences between the arms beyond 3 years that may be particularly compelling to drive practice changes and patient decisions should the two approaches be reasonably similar in terms of disease control. In particular, as detailed in Section 11.1.1, prior studies on breast pain after radiotherapy in historical trials from Sweden have shown effects that are present 10-17 years after treatment; findings of differences in pain at 5 years might be especially meaningful to patients as they indicate a particularly long lasting effect (but outcomes with modern radiotherapy are not known and merit evaluation in this study). Moreover, as described in Section 2.4, worry about recurrence influences patient decisions, and the long term levels of worry across two randomized arms could be particularly meaningful for women facing these decisions. Multiple studies have shown that cosmetic decrement due to radiotherapy continues to evolve many years after its completion, including analyses of NRG trials and NCIC trials. Additionally, most of these women will receive endocrine therapy recommendations for at least 5 years of treatment, so understanding their long-term experiences and reasons for non-adherence, along with symptoms associated with endocrine therapy, merit consideration.

11.3 Administration of BR007 Patient-Completed Questionnaires

11.3.1 Time points for Administration

The BR007 HRQOL questionnaire (Form HRQOL) will be administered via the Medidata Patient Cloud (eCOA/ePRO) mobile app at the following time points:

- Prior to study entry after the BR007 consent form has been signed, and eligibility has been confirmed.
- Following study entry:
  - 6 months
  - 12 months
  - 24 months
  - 36 months
  - 48 months
  - 60 months

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11.4 Administration Instructions

For patients who complete the questionnaires on-site using devices supplied by the institution, after the baseline assessment, questionnaires are to be administered at follow-up visits, so that when a follow-up visit is delayed, completion of the HRQOL questionnaire may also be delayed. HRQOL assessments should be discontinued at the time of disease progression. The HRQOL questionnaire should be administered during an office visit if at all possible, preferably while the patient is waiting to be seen. If unable to complete the QOL questionnaires via ePRO, the QOL may be completed via paper and manually entered into Rave by site staff. The paper forms should not be submitted to NRG Oncology but should be retained in the patient's chart for audit purposes.

Patients who never initiate BR007 study therapy or discontinue study therapy for reasons other than disease progression are expected to continue the HRQOL assessments on schedule. It is acceptable to conduct these assessments by telephone if necessary.

If a patient declined to complete a scheduled HRQOL assessment or if the assessment is not completed for any other reason (and cannot be completed by phone), the reason the assessment was missed must be reported on the QOL Coversheet in Medidata Rave.

11.5 HRQOL Patient Population

All patients enrolled in BR007 who read or understand English must be offered participation in the HRQOL study. HRQOL will be evaluated in 290 consecutively enrolled BR007 patients who have completed the baseline questionnaire. If a patient chooses to not complete the baseline HRQOL questionnaire or if completion of the baseline questionnaire is missed, the patient will not be included in the HRQOL patient sample but will still be eligible for BR007.
12.0 DOCUMENTATION OF BREAST CANCER RECURRENCE AND OTHER CANCER EVENTS

12.1 General Instructions

- Documentation of a breast cancer recurrence requires meeting at least one of the criteria defined below. Suspicious findings do not provide adequate documentation of a breast cancer recurrence, and should not be an indication to alter protocol therapy.
- Tumor marker evaluations alone do not document breast cancer recurrence.
- Treatment of a breast cancer recurrence or second primary cancer will be at the discretion of the investigator.

12.2 Local Recurrence

Note: If the first local recurrence is non-invasive breast cancer, the first invasive breast cancer must also be reported.

Recurrent local tumor is defined as evidence of invasive breast cancer or DCIS in the ipsilateral breast or invasive breast cancer in the skin of the ipsilateral breast. Patients who develop clinical evidence of local recurrence in the ipsilateral breast must have a biopsy confirmation of recurrence. However, if a patient also meets criteria for regional or distant metastatic disease, results of clinical exams alone will be sufficient to document local recurrences.

12.2.1 Ipsilateral breast tumor recurrence (IBTR)

An IBTR event is defined as recurrent invasive breast cancer or DCIS in the ipsilateral breast parenchyma or invasive breast cancer in the skin of the breast occurring after lumpectomy.

Acceptable documentation includes core, incisional or excisional biopsy. Cytology alone will not be adequate to establish IBTR.

12.2.2 Other local recurrence

Defined as recurrence in the skin of the chest wall (exclusive of the breast) or chest wall.

Acceptable documentation includes core, incisional or excisional biopsy, as well as cytology.

12.3 Regional Recurrence

Defined as the development of tumor in the ipsilateral internal mammary, ipsilateral suprACLavicular, ipsilateral infraclavicular and/or ipsilateral axillary nodes, as well as the soft tissue of the ipsilateral axilla, following surgery. Recurrence must be confirmed by biopsy or cytology. However, if a patient meets the criteria for distant metastatic disease, results of clinical exams alone will be sufficient to document regional recurrences.

12.4 Distant Recurrence

Defined as evidence of tumor in all areas, with the exception of those described in Sections 12.2 and 12.3. The first distant recurrence and the first central nervous system recurrence will be
reported. Further treatment for distant metastasis, with or without evidence of local-regional recurrence, will be at the discretion of the investigator.

12.4.1 Skin, subcutaneous tissue, and lymph nodes (other than local or regional)

Acceptable documentation includes positive cytology, aspirate or biopsy, or radiologic evidence of metastatic disease.

12.4.2 Bone Marrow

Acceptable documentation includes positive cytology, aspirate, biopsy, or MRI scan.

12.4.3 Lung

Acceptable documentation includes: (i) positive cytology, aspirate, or biopsy, or (ii) radiologic evidence of multiple pulmonary nodules that are judged to be consistent with pulmonary metastases.

Note: If a solitary lung lesion is found and no other lesions are present on lung tomograms, CT scan, or MRI scan, further investigations, such as biopsy, needle aspiration, or PET-CT scan should be performed. Proof of neoplastic pleural effusion must be established by cytology or pleural biopsy.

12.4.4 Skeletal

Acceptable documentation includes: (i) x-ray, CT, or MRI evidence of lytic or blastic lesions consistent with bone metastasis, (ii) biopsy proof of bone metastases, or (iii) bone scan, or PET-CT scan clearly positive for bone metastases.

Note: If the diagnosis is equivocal by bone scan or radiologic evaluation, a biopsy is strongly recommended. A bone scan with uptake limited to joints or in a recent area of trauma (surgical or otherwise) cannot be used as a criterion for breast cancer recurrence.

12.4.5 Liver

Acceptable documentation includes: (i) abdominal CT scan, liver scan, ultrasound, MRI, or PET-CT scan consistent with liver metastases, or (ii) liver biopsy confirmation of the metastatic disease.

Note: If the radiologic findings are not definitive (especially with solitary liver nodules), a liver biopsy is recommended; however, if a biopsy is not performed, serial scans must be obtained to document stability or progression.

12.4.6 Central Nervous System

Acceptable documentation includes: (i) positive CT scan, PET-CT scan or MRI scan, usually in a patient with neurological symptoms, or (ii) biopsy or cytology (for a diagnosis of leptomeningeal involvement).
12.5 **Contralateral Breast Cancer**

Contralateral breast cancer is defined as evidence of invasive breast cancer or DCIS in the contralateral breast or chest wall. The diagnosis of a contralateral breast cancer must be confirmed by core, incisional, or excisional biopsy. Cytology alone will not be adequate to document a contralateral breast cancer.

12.6 **Second Primary Cancer**

Second primary cancer is defined as any invasive non-breast cancer other than squamous or basal cell carcinoma of the skin. The diagnosis of a second primary cancer must be confirmed histologically whenever possible.

12.7 **Documentation Requested Following Death**

- Autopsy reports should be secured whenever possible and should be submitted to the NRG Oncology SDMC.
- A copy of the death certificate should be forwarded to the NRG Oncology SDMC if it is readily available or if it contains important cause-of-death information that is not documented elsewhere.
- Please submit the last clinic/office note made before the death or the investigator’s note summarizing events resulting in death.
13.0 DATA AND RECORDS

13.1 Data Management/Collection

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

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (Lab Admin), Rave SLA or Rave Investigator.
- Rave role requirements:
  - Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate plus (AP) registration type;
  - Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
  - Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to [https://ctep.cancer.gov/InvestigatorResources/default.htm](https://ctep.cancer.gov/InvestigatorResources/default.htm) for registration types and documentation required.

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

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at [www.ctsu.org/RAVE/](http://www.ctsu.org/RAVE/) or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctstucontact@westat.com.

HRQOL and PRO items will be collected using the Medidata Patient Cloud (eCOA/ ePRO) mobile app. The patient will use personal hand-held devices or tablets. Once a patient submits the responses, the data goes directly from the device into the Rave database. There are no documents to audit. The electronic responses are the source documentation.

13.2 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled
times during the trial using Medidata Rave. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7.5 and Section 7.6 for information about expedited and routine reporting.

Summary of Data Submission: Refer to the CTSU Member website for the table of Required Forms and Materials.

Endocrine adherence will be collected for all patients on a coordinator completed form which will be included with the Required Forms and Materials on the CTSU Member website.

13.3 Data Quality Portal

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

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

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

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

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

Complications or unexpected outcomes reporting is required as part of this clinical trial, to ensure the safety of participants enrolled in the studies as well as those who will enroll in future studies. See Section 7.0 for information about reporting complications or unexpected outcomes.

13.4 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period and used to collect AEs that start during the period or persist from the previous reporting period. The CRA will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:
- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence, that Internet connectivity is lost; a 24-hour notification is to be made to the NRG Oncology Statistics and Data Management Center by telephone at 412-624-2666. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:
- Study specific documents: Protocols > Documents > Education and Promotion; and

NCI requirements for SAE reporting are available on the CTEP website:

13.5 Global Reporting/Monitoring

*For studies assigned Demography monitoring and enrolling patients via OPEN:*

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

**Note:** Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.
### Summary of Dosimetry Digital Data Submission

Submit Digital RT Data via TRIAD; see Section 8.5 for TRIAD account access and installation instructions.

| DICOM DIGITAL DATA | DICOM CT IMAGE SET | TRIAD submission time point  
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</table>

All required structures MUST be labeled per the tables in Section 5.4.4

Upon submission of the Digital Data via TRIAD, complete an online Digital Data Submission Information Form (DDSI) [https://www.irocqa.org/Resources/TRIAD](https://www.irocqa.org/Resources/TRIAD)
14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design

Eligible patients will be randomized 1:1 to post lumpectomy to radiation therapy versus no radiation therapy. Randomization will be stratified by Age (< 60; ≥ 60), RS (≤ 11, > 11), and Tumor size (≤ 1 cm; 1.1-2 cm).

14.2 Study Endpoints

14.2.1 Primary Endpoint

Time to invasive or noninvasive IBTR.

14.2.2 Secondary Endpoints

Secondary endpoints of this study are:

- Percent of women with an intact index breast at report of the primary endpoint inclusive of salvage second breast conservation procedures.
- Time from randomization to the first occurrence of invasive ipsilateral breast tumor recurrence.
- Time from randomization to diagnosis of a local, regional or distant recurrence as a first cancer event.
- Time from randomization to the first distant cancer event (either a recurrence or a secondary primary cancer).
- Time from randomization to any death.

14.3 Primary Objective and Primary Hypothesis

14.3.1 Primary Objective

To evaluate whether breast conservation surgery and endocrine therapy results in a non-inferior rate of ipsilateral-breast tumor recurrence (IBTR) compared to breast conservation with breast radiation and endocrine therapy.

14.3.2 Primary Hypothesis

Breast conservation surgery and endocrine therapy results in a non-inferior rate of invasive or non-invasive ipsilateral-breast tumor recurrence (IBTR) as compared to breast conservation, breast radiation, and endocrine therapy.

14.3.3 Power Justification Expected Sample Size and Accrual Estimates

Our projected event free survival (EFS) for IBTRs in the RT group was based on 9–year results in the TailorX trial for patients with similar recurrence scores in that study. Because our conversations were based on typical landmark times, we first calculated the 10-year event–free survival (EFS) for the RT group as $\lambda_{RT} = -\ln(0.96)/10 = 0.004536 \Rightarrow EFS_{RT} = \exp\{-\lambda_{RT}\times10\} \approx 0.956$. If the EFS in the No RT group is ≤ 4% worse than that of the RT group, we will declare equivalence. Letting $\Delta = .04$ we have the upper bound of the event rate of the No RT as $\lambda_{No\ RT} \approx 0.008812$. Thus, the boundary hazard ratio (HR) at 10 years is $HR \approx .008812/.004536 \approx 1.943$. We used this boundary HR and assumed that $\alpha = 0.025$, that there would be 1% loss to follow-up
each year of the study and that there would be a ramp–up in accrual in the first two years of the study (leveling off from Years 3 – 5). If we have randomized 1670 patients (835 in each group), we will have 80% power at an average of 10 years of cohort follow–up (Calendar Year 13 of the study) to detect an equivalence HR ≈ 1.943 when the equivalence hazard ratio is 1.00 and the reference group hazard rate is λRT ≈ 0.004537. Framing this HR as differences in EFS for IBTR, this is equivalent to declaring any EFS value in the No RT group ≥ 91.57% at 10 years of average follow-up being equivalent to that of the RT group (assuming that the EFS RT group was about 95.57%). The number of required events for equivalence is 36 in each group, we would do a definitive analysis when 72 events had been reported in the group. If less than 72 events have been reported as of Year 14 of the study, a definitive endpoint analysis will be performed with the number of events reported at that time. It should be noted that some of the T1a patients accrued to this study will have oncotype DX scores > 18 making them ineligible for the study. Based on B-39 data, about 10.4% of the T1 patients are expected to be T1a and we conservatively inflate the number in that sub-cohort by 20% to achieve the requisite number of patients having an oncotype DX score ≥18. Hence, our patient recruitment at Step 1 of the accrual process will be inflated to \(1670 \times (0.104/0.80 + 0.896)\) ≈ 1714 patients to be accrued to ensure our final randomized cohort includes 1670 patients.

### 14.4 Statistical Analyses

The occurrence of the definitive analysis will be event driven. An interim analysis will be performed when 1/3 of the study information is available in the study, that is, when 24 events have been reported. If the analysis at that point reveals that the HR of the No RT group compared to the RT group is significantly greater than the equivalence boundary HR of 1.943 based on a one-sided p-value of 0.05, then a recommendation to the study DMC will be made to divulge the study primary endpoint results. Another interim analysis will be conducted when 50% of the endpoint information has been recorded, i.e., when 36 IBTR events have been reported. This second interim will follow the Wieand rule (Wieand 1994), that is, if the HR exceeds 1.943, even if the value is not statistically significant then a recommendation to the study DMC will be made to divulge the study primary endpoint results. In addition, as part of the report to the interim reports to the DMC and the final analysis, we will report the proportion of patients in the No RT arm who “cross over”, that is, receive RT prior to experiencing an event; the proportions of patients assigned to RT but who refuse RT; and the proportions of patients in each arm who fail to receive at least 5 years of endocrine therapy. These non-compliance proportions will be reported for all randomized patients and also, separately by recurrence score within each arm.

The intention-to-treat (ITT) principle will be used for the primary analysis of the study endpoints. Accordingly, the analyses will be performed on all patients with follow-up regardless of eligibility or compliance status and will use the treatment assignments made at randomization. To evaluate the compliancy of the endocrine therapy in the trial, a dynamic approach using a Kaplan-Meier type analysis of adherent patients will be employed. A log-rank test will be used to compare adherence rates between the two groups.

As secondary analyses, per protocol analyses will be repeated on patients with follow-up who are eligible for the study and who are 80% compliant with protocol therapy.

For the primary endpoint, the formal point estimates of the group IBTR-free survival will be performed with Kaplan-Meier techniques and inference made by a log-rank test. If the upper bound of the two-sided 90% HR confidence interval for IBTR EFS is ≤ 1.943, then the No RT group will be declared to be non-inferior to the RT group. Further analyses will be carried out to assess the influence of the competing risk of death on IBTR event rate point estimates, using cumulative incidence curves (Gaynor 1993) and competing risks analyses (Fine 1999) will be performed to compare rates of IBTR. We will test heterogeneity of treatment effects for each of
the stratification variables. Standard log-rank methodology will be used to analyze the OS endpoint. Competing risks methodology will also be applied to the IRFI endpoint because of the competing risk of death from any cause.

14.5 Statistical Considerations for HRQOL Study

14.5.1 HRQOL Sample Size

Since we have two primary HRQOL endpoints, the significance level must be split to account for multiple comparisons. We estimate that a sample of 202 patients would provide 90% statistical power to detect a difference of 0.5 standard deviations between groups with significance level at 0.025. After adjusting upward to account for a 30% dropout or missing data rate, we would need to enroll 290 participants in the HRQOL study.

The secondary HRQOL hypothesis addressing global quality of life is based on a non-inferiority test for the difference between two means. Our sample size of 202 patients would provide 81% power to detect non-inferiority of omission of radiation therapy, assuming that the two-sided probability of type 1 error is 0.05 and the margin of non-inferiority is 40% of the standard deviation of the average score.

14.5.2 HRQOL Analyses

The primary aims of the HRQOL sub-study are to evaluate whether there are differences in patient-reported breast pain or worry about breast recurrence in women who do and do not receive breast radiation. For the first primary hypothesis, the BCTOS pain subscale score measured at 3 years after randomization will be compared between the two study arms using analysis of covariance (ANCOVA) adjusting for the corresponding baseline (pre-randomization) measurement. For the other primary hypothesis, the three-item worry about recurrence score measured at 3 years will also be compared between the study arms using ANCOVA with adjustment for the corresponding baseline measure. Each comparison will be performed at the significance level of 0.025.

For the secondary analyses, the BCTOS functional status score, the BCTOS cosmesis score, the Global Cosmesis Score, and the PROMIS global physical and mental health scores measured at 3 years after randomization will be compared between the study arms using ANCOVA with adjustment for the corresponding baseline measure. Additionally, the PROMIS fatigue score and breast cancer treatment symptom scores measured at six months after randomization, and the Voils adherence scores measured at 5 years after randomization will be compared between the study arms using ANCOVA with adjustment for the corresponding baseline measure.

As exploratory analyses, the pattern of all measured HRQOL scores will be assessed over time using mixed effects longitudinal models. These models will be used to test whether or not trends in HRQOL scores occur over time and whether those trends are different, that is, whether there are treatment-by-time interactions.

All secondary analyses will be performed at 0.05 alpha level and the clinical meaningfulness of all comparisons will be considered.

14.5.3 Missing HRQOL Data

A certain amount of missing data is expected; however, we have extensive experience in the collection of patient-reported outcome data with excellent adherence to data collection across multiple studies as such data are considered as part of institutional performance metrics.
Prospective calendars and reminder systems are in place to ensure collection of these data. Proportions of missing data over visits will be assessed using Kaplan-Meier methods similar to those being used to assess hormonal treatment adherence. The information from patients with missing data will be reviewed in order to determine whether data analytic procedures are likely to be biased. Patients with missing data will be reviewed for imbalances in factors such as trial arm, treatment adherence, institution, and reason for non-adherence. When HRQOL data are missing at a particular time point, data from prior time points will be reviewed in order to investigate whether missing status was preceded by a significant change in HRQOL scores. In addition, we will investigate whether missing item status is related to other scores on the same questionnaire. If no missing data mechanism can be detected following this review, the data will be analyzed assuming that the data are missing at random. If, on the other hand, a non-random missing data mechanism appears to be present, we will undertake to develop an appropriate analytic strategy to control for the potential bias. We will also present sensitivity analyses based on varying assumptions about the missing-data mechanism.

14.6 Gender/Ethnicity/Race Distribution

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.
### DOMESTIC PLANNED ENROLLMENT REPORT

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<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Female</td>
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<td>0</td>
</tr>
<tr>
<td>Male</td>
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<td>0</td>
</tr>
<tr>
<td>Female</td>
<td>1268</td>
<td>0</td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1452</strong></td>
<td><strong>0</strong></td>
</tr>
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</table>

### INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT

<table>
<thead>
<tr>
<th>Racial Categories</th>
<th>Ethnic Categories</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not Hispanic or Latino</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>American Indian/ Alaska Native</td>
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<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
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<td>0</td>
</tr>
<tr>
<td>Black or African American</td>
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<td>0</td>
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<tr>
<td>White</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>147</strong></td>
<td><strong>0</strong></td>
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</table>
Table 21B. Expected racial and ethnic composition of NRG-BR007 Accrual Cohort

### DOMESTIC PLANNED ENROLLMENT REPORT

<table>
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<tr>
<th>Racial Categories</th>
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<tr>
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<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
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<td>Black or African American</td>
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<td>0</td>
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<td>White</td>
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<td>Other</td>
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### INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT

<table>
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<th>Racial Categories</th>
<th>Ethnic Categories</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not Hispanic or Latino</td>
<td>Hispanic or Latino</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
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<td>0</td>
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<tr>
<td>Asian</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Black or African American</td>
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<td>0</td>
</tr>
<tr>
<td>White</td>
<td>147</td>
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<td>0</td>
</tr>
<tr>
<td>Total</td>
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</tbody>
</table>
REFERENCES


APPENDIX A
ASSESSMENT OF PERFORMANCE STATUS AND ACTIVITIES OF DAILY LIVING

1.0 PERFORMANCE STATUS

<table>
<thead>
<tr>
<th>ECOG or Zubrod Scale</th>
<th>Fully active; able to carry on all pre-disease performance without restriction</th>
<th>Karnofsky Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90-100%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory</td>
<td>70-80%</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of self-care; but unable to carry out any work activities</td>
<td>50-60%</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care; confined to bed or chair more than 50% of waking hours</td>
<td>30-40%</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled</td>
<td>10-20%</td>
</tr>
</tbody>
</table>

2.0 ACTIVITIES OF DAILY LIVING

The following definitions for activities of daily living (ADL) should be used when the CTCAE v5.0 grading criteria are based on ADL:

- **Instrumental ADL** refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- **Self-care ADL** refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
APPENDIX B
BR007 CONTOURING GUIDELINES

1. CONTOURING TARGETS AND ORGANS AT RISK (OAR):
   a. Targets

<table>
<thead>
<tr>
<th>Standard Name</th>
<th>Description</th>
<th>Delineation guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV_Lump</td>
<td>gross tumor volume (GTV) for Lumpectomy</td>
<td>Contour the lumpectomy bed as apparent on planning image. Use surgical clips or fiducials when present. Can include the excision cavity volume, architectural distortion, seroma.</td>
</tr>
<tr>
<td>CTV_Lump</td>
<td>lumpectomy CTV; clinical tumor volume (CTV) including regions of the GTV suspicious for subclinical disease</td>
<td>Include the lumpectomy GTV plus 1.0 cm to 1.5 cm of surrounding breast tissue, but exclude the pectoralis muscle, all chest wall muscles, ribs, contralateral breast, and regions exterior to the patient surface. For APBI 1.5 cm expansion on GTV recommended.</td>
</tr>
<tr>
<td>PTV_Lump</td>
<td>lumpectomy PTV</td>
<td>lumpectomy CTV + 0.5 cm (if IGRT used) or 0.7 cm (if no IGRT) expansion in all directions; exclude heart and lung</td>
</tr>
<tr>
<td>PTV_Lump_EVA</td>
<td>PTV evaluation volume; PTV minus overlapping critical structure ROIs; relevant regarding boosts to the lumpectomy site</td>
<td>recede PTV_Lump by 0.3 to 0.5 cm distal to the skin surface, do not extend beyond breast tissue, and do not cross midline</td>
</tr>
<tr>
<td>CTV_WB</td>
<td>whole breast CTV; ipsilateral (to be treated) breast</td>
<td>include the glandular breast tissue as apparent on the planning image, incorporating the anatomic borders as summarized in this Appendix and include the entire lumpectomy CTV</td>
</tr>
<tr>
<td>PTV_WB</td>
<td>whole breast PTV; ipsilateral (to be treated) breast</td>
<td>whole breast CTV + 0.5 cm (if IGRT used) or 0.7 cm (if no IGRT) 3D expansion; exclude heart and lung; do not cross midline</td>
</tr>
<tr>
<td>PTV_WB_EVA</td>
<td>whole breast PTV evaluation volume; ipsilateral (to be treated) breast</td>
<td>recede PTV_WB by 0.3 to 0.5 cm distal to the skin surface</td>
</tr>
</tbody>
</table>

   a. Organs at Risk (OAR)

   The OAR to be contoured on all cases:
   1. Ipsilateral lung
   2. Contralateral lung
   3. Heart
   4. Contralateral breast
   5. Thyroid
2. GUIDELINES FOR CONTOURING TARGETS – WHOLE BREAST IRRADIATION

Post lumpectomy standard of care Whole breast irradiation + boost, Partial breast irradiation, and Accelerated Partial Breast Irradiation is acceptable for treatment in ARM 1 on this trial. The targets outlined below are for guidance as needed.

1.1 Lumpectomy Target Volumes

2.1.1 Lumpectomy cavity (GTV_Lump): (Figure 1.a. Supine, 1.b. Prone). The term “lumpectomy” will represent the surgical cavity from the breast conserving surgery. 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).

2.1.2 Lumpectomy Clinical Target Volume (CTV_Lump): (Figure 1.a. Supine, 1.b. Prone). The Lumpectomy CTV typically consists of the contoured GTV-Lump plus a 1 – 1.5 cm 3D expansion. The extent of expansion will be per the investigators’ discretion based on extent of risk. A minimum expansion of 1 cm is recommended. In general, the CTV_Lump is limited posteriorly at anterior surface of the pectoralis major and anterolaterally 5 mm from skin. For medially place surgical cavities, the CTV_Lump expansion should not cross midline. In general, the pectoralis muscles, latissimus and/or serratus anterior muscles are excluded from the CTV_Lump unless clinically warranted by the patient’s pathology.

2.1.3 Lumpectomy Planning Target Volume (PTV_Lump): (Figure 2.a Supine, 2.b. Prone). The lumpectomy PTV is typically a 5-7 mm expansion on the Lumpectomy CTV and is based on the institutions variation in day – to day setups. It excludes the heart. This is the structure used for beam aperture generation.

2.1.4 Lumpectomy Planning Target Volume for Evaluation (PTV_Lump_EVA): (Figure 3.a. Supine, 3.b. Prone). This Lumpectomy PTV_EVAL is limited to exclude the portion of the PTV that extends outside the ipsilateral breast beyond skin or into the chestwall 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. a. Supine Lumpectomy (GTV_lump) and Lumpectomy Clinical Target Volume (CTV_lump)

Figure 1. b. Prone Lumpectomy and Lumpectomy Clinical Target Volume
Figure 2. a. Supine Lumpectomy Planning Target Volume (PTV-Lump)

Figure 2. b. Prone Lumpectomy Planning Target Volume (PTV_Lump)
Figure 3. a. Lumpectomy Planning Target Volume for Evaluation (PTV_Lump_EVA)

Figure 3.b. Lumpectomy Planning Target Volume for Evaluation (PTV_Lump_EVA)
2.2 Breast Target Volumes

2.2.1 Breast Clinical Target Volume (CTV_WB): (Figure 4.a. Supine, 4.b. Prone). 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 serratus anterior muscles/chestwall are excluded from the breast CTV unless clinically warranted by the patient’s pathology. NRG RTOG anatomy consensus guidelines are available at: https://www.nrgoncology.org/Portals/0/Scientific%20Program/CIRO/Atlases/BreastCancerAtlas_corr.pdf.

2.2.2 Breast Planning Target Volume (PTV): (Figure 4.a. Supine, 4.b. Prone). 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.a. Supine, 5.b. Prone). The Breast PTV_EVAL is intended to exclude the portion of the breast PTV that extends 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.a. Supine Breast Clinical Target Volumes (CTV_WB) and Breast Planning Target Volumes (PTV_WB)
Figure 4.b. Prone Breast Clinical Target Volumes (CTV_WB) and Breast Planning Target Volumes (PTV_WB)

Figure 5.a. Supine. Breast Planning Target Volume for evaluation (PTV_WB_EVA)
3 GUIDELINE for ACCELERATED PARTIAL BREAST IRRADIATION and PARTIAL BREAST IRRADIATION

3.1 Lumpectomy Target Volumes

3.1.1 Lumpectomy cavity (GTV_Lump): (Figure 6.a. Supine, 6.b. Prone). The term “lumpectomy” will represent the surgical cavity from the breast conserving surgery. 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).

3.1.2 Lumpectomy Clinical Target Volume (CTV_Lump): (Figure 6.a. Supine, 6.b. Prone). The Lumpectomy CTV typically consists of the contoured GTV-Lump plus a 1.5 – 2.0 cm 3D expansion. The extent of expansion will be per the investigators’ discretion based on extent of risk. A minimum expansion of 1.5 cm is recommended. In general, the CTV_Lump is limited posteriorly at anterior surface of the pectoralis major and anterolaterally 5 mm from skin. For medially placed surgical cavities, the CTV_Lump expansion should not cross midline. In general, the pectoralis muscles, latissimus and/or serratus anterior muscles are excluded from the CTV_Lump unless clinically warranted by the patient’s pathology.

3.1.3 Lumpectomy Planning Target Volume (PTV_Lump): (Figure 7.a Supine, 7.b. Prone). The lumpectomy PTV is typically a 5-7 mm expansion on the Lumpectomy CTV and is based on the institutions variation in day – to – day setups. It excludes the heart. This is the structure used for beam aperture generation.

3.1.4 Lumpectomy Planning Target Volume for Evaluation (PTV_Lump_EVA): (Figure 8.a. Supine, 8.b. Prone). The PTV_Lump_EVA excludes the first 5 mm of tissue under the skin (in order to remove most of the buildup region for the DVH analysis) and excludes the 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 6. a. Supine Lumpectomy (GTV_lump) and Lumpectomy Clinical Target Volume (CTV_lump) for APBI, PBI

Figure 6. b. Prone Lumpectomy (GTV_lump) and Lumpectomy Clinical Target Volume for APBI, PBI
Figure 7. a. Supine Lumpectomy Planning Target Volume (PTV-Lump) APBI, PBI

Figure 7. b. Prone Lumpectomy Planning Target Volume (PTV-Lump) APBI, PBI
Figure 8.a. Supine. Lumpectomy Planning Target Volume for Evaluation (PTV_Lump_EVA) APBI, PBI

Figure 8.b. Prone. Lumpectomy Planning Target Volume for Evaluation (PTV_Lump_EVA) APBI, PBI
4. **Breast Reference Volume for APBI, PBI**

Clinical extent of the breast excluding chestwall, muscles, ribs and OAR (heart and lung). The PTV_lump_EVA volume for APBI or PBI should be < 25% whole breast reference volume.

Figure 9. a Supine. Whole breast reference volume APBI, PBI

Figure 9. b. Prone. Whole Breast Reference Volume APBI, PBI
APPENDIX C
MEDIDATA PATIENT CLOUD ePRO OPERATIONAL PROCEDURES

In this document ePRO application refers to the application accessed by the site via iMedidata and Rave, and ePRO mobile app refers to the app accessed by the patient on a mobile device.

1.0 Introduction

Electronic collection of patient-reported outcomes (ePRO) through the Medidata's ePRO application is preferred but not mandatory for patients who read or understand English. Traditional paper submission is the other option. Sites are not permitted to delete the ePRO component from the protocol or from the sample consent. Patients who will be submitting PRO data via the ePRO mobile app must be registered to the ePRO application by an authorized site staff after the patient has been registered to the study. Patients may use their own device or one provisioned by the site.

Sites can use a site-specific tablet for multiple study participants. If a site-specific tablet is used, CRAs need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log in to Patient Cloud ePRO with their passwords or their PIN codes on the same device.

2.0 ePRO Mobile Application Download

Note that there are multiple versions of the ePRO mobile app. Patients should be instructed to download the version chosen by the study team for the protocol. The patient will receive an error upon logging into the ePRO mobile app if the wrong version is downloaded. The version being used on this trial is:

Patient Cloud

3.0 CRA Site Users

Site staff require access to the ePRO application. This access is granted through the iMedidata and is similar to the process of obtaining access to Rave studies. Site staff will receive an invitation to the ePRO application which they must accept in order to begin registering patients. Staff who have not previously activated their iMedidata/Rave account at the time of initial approval of site registration will also receive a separate invitation from iMedidata to activate their account. Medidata Account Activation and Study Invitation Acceptance instructions are located on the CTSU members' website, under Data Management > Rave Home > Learn More About Rave > Medidata Account Activation and Study Invitation Acceptance. Site staff will not be able to access the study in the ePRO application until all required Rave and study specific trainings are completed (eLearnings assigned in iMedidata) are completed.

Additional information on iMedidata/Rave is available on the CTSU members’ website under the Data Management tab and further under the Rave subtab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at etsucontact@westat.com.

4.0 CRA Instructions for Setting the Patient Cloud Mobile App to Multi-User Mode

Sites conducting studies entirely on-premise, where participants travel to the sites to fill out questionnaires, can use multi-user mode. Multi-user mode lets multiple study participants log in to the ePRO mobile app with their passwords or their PIN codes on the same device. If patients will be using devices supplied by the institution, site staff will need to help the patient to access the device if the device is locked.
The study provider will download the ePRO mobile app to the device and set the ePRO mobile app to multi-user mode if applicable. **Verify the correct ePRO mobile app (Patient Cloud OR Patient Cloud ePRO) is downloaded per the protocol requirements. Note only 1 version of the app is active per protocol. On this protocol the app is named Patient Cloud and its icon is:

![Patient Cloud](image)

To switch from personal mode (default setting) to multi-user mode:

1. Tap **About** at the bottom of the log in screen.
2. Scroll to the bottom and tap **Advanced User**.
3. Tap **Mode**, then select **Multi-User**.
4. Tap **Yes** to confirm.
5. Tap the back arrows to return to the log in screen.

**Note:** If enabling multi-user mode on a device, it is highly recommended that completion reminders are turned off on that device.

5.0 **Patient Users**

To use the ePRO mobile app, patients will need to use their own device (IOS, Android phone, or tablet) or one provided at the site. For instructions for patients using their own device refer to section #6 below. Short term data will only appear on the patient’s device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the “Submit” button and will no longer be visible on the patient's device.

Sites can provide a site-specific tablet for multiple study participant use on site. If a site-specific tablet is used, study staff need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log into the ePRO mobile app with their passwords or their PIN codes on the same device. **Refer to Section 4.0 above on Setting the Patient Cloud App to Multi-User Mode.**

6.0 **Patient Instructions for Accessing the Patient Cloud Using Your Personal Device**

**Downloading the Patient Cloud ePRO Mobile App**

If you are using your personal device, and you do not have the ePRO mobile app with the icon shown below, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. If the ePRO mobile app is already on the device, or if you are using a provider's device, you can skip this section. There are multiple versions of the ePRO mobile app available. Ensure that the correct version of the ePRO mobile app is downloaded. For this study the app is named Patient Cloud and its icon looks like this:

![Patient Cloud](image)

You will need an email address that you agree to use for this purpose. The email address is needed to uniquely identify you on the ePRO Application, and to reset your password if needed. Your email address will only be used for this survey study and will not be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an email address, you may sign up for one at no charge at many different websites. A few sites that
are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS (when using an Apple device):
1. An Apple ID is required for downloading the ePRO mobile app.
2. Tap the App Store icon.
3. Search for the appropriate ePRO mobile app ("Patient Cloud", see the icon above) and follow the installation instructions.

For Android:
1. A Google account is required for downloading the ePRO mobile app.
2. Tap the Play Store icon.
3. Search for the appropriate ePRO mobile app ("Patient Cloud", see the icon above), and follow the installation instructions.

Registering

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the ePRO mobile app.

Note: You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the ePRO mobile app.

1. If registering from the ePRO mobile app, open the Patient Cloud app, tap Register on the bottom of the log in page. If registering on the web, open the URL shield.imedidata.com on a web browser.
2. Enter your activation code and tap Activate.
3. On the next page, read the instructions and tap Next.
4. Read the privacy notice and tap I agree. Then tap OK to confirm.
5. Enter and confirm your email address. Tap Next.
6. Enter and confirm your password. Tap Next.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap Create my account to complete your registration.

If you registered on the ePRO mobile app, it automatically logs you out. If you registered on the web, you are presented with the option to download the ePRO mobile app (Patient Cloud). You can then proceed to log in with the credentials you created.

Logging in to the ePRO Mobile App

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

Note: If you do not remember your password, tap Forgot Password, and follow the instructions provided.
Setting a PIN Code

The first time you log in to the ePRO mobile app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the ePRO mobile app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap Forgot PIN and you can access the app using your email and password. You may reset your PIN by tapping the options menu (3 vertical dots) on the top right of most pages and selecting Set PIN.

Resetting Your Password

You can reset your password by using the options menu at the top right of most pages.

1. Tap the Options menu icon (3 vertical dots).
2. Tap Reset Password.
3. Follow the instructions to reset your password.

Completing and Submitting Forms

Once logged into the ePRO mobile app, forms related to your study are displayed on the Tasks List page. Select a form, and complete and submit the form. New forms can appear on the Tasks Lists page at any time, depending on how the study is designed.

There are two types of forms displayed on the Tasks List page:

- **Scheduled Forms** (with a icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.

- **Anytime Forms** (with a icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an "Incomplete" status beneath the form name, along with a half-moon icon.

To complete and submit form(s):

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you may be given the opportunity to review and change your responses prior to submitting.
3. If given the opportunity to review and update, review your responses by scrolling down the list. If you need to change an answer, tap the question to go back and change the answer.
4. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

7.0 Patient Compliance

The patient data imports directly from a device into the Rave database. There are no documents to audit. The patient-submitted electronic responses are the source documentation.
8.0 Security

All data is encrypted on the device (256 bit encryption and Hyper Text Transfer Protocol Secure [https]) and the app requires each user to have a unique username and password for access. If the user is idle for too long (5 minutes inactivity time), the app will time out, and the user will need to log in again.

The data will only reside on the device for a short period of time. Once the user clicks “Submit,” the data is securely transferred over HTTPS between the device and internal relay to the Rave database. Except for the patient's email address, no identifying information is stored in iMedidata. The email is stored for what purpose? The patient's email links the device (used) and (ePRO) account to where the data is stored. The patient's email is not visible to anyone in the system.

The Patient information (email/password) does not reside in Medidata Rave EDC, and the patient accounts are hidden in iMedidata from sites and LPOs.

The ePRO application is 21 CFR Part 11 compliant and acts as a gateway between the device and Medidata Clinical Cloud (MCC).

Messages and information communicated to and from the Patient Cloud app are encrypted and therefore this information cannot be read if intercepted while in transit.

9.0 Site checklist for activities prior to consenting a patient

- Accept study invitation at iMedidata.com.
  - Site staff must be rostered in RSS and have received an invitation to the ePRO application.
- Site staff must have already completed required eLearning assigned in iMedidata for the ePRO application before gaining access to the study in Rave. Contact the LPO to request appropriate Rave access to register patients in the ePRO application.
- Verify the IOS or Android operating system is using the most current version.
- Verify that the correct ePRO mobile app is being used.
  - Note only 1 version of the ePRO mobile app is active per protocol.
- If using institutional shared devices, first patient only: Verify ePRO mobile app is in Multi-User mode.
- See the following webpage for more information about Patient Cloud iOS and Android ePRO apps. The landing page contains general information as well as links to additional resources on the left side of the screen [https://learn.mdsol.com/patient-cloud/ecoa/en/switch-to-multi-user-mode-216933032.html](https://learn.mdsol.com/patient-cloud/ecoa/en/switch-to-multi-user-mode-216933032.html).

Note: Sites should consider copying this site checklist and placing it in the clinic or area where site is consenting patients to ePRO and also copy the correct image and name of the ePRO mobile app version with it to help remind staff and patients of the correct version being used in the protocol. The correct version for this protocol is named “Patient Cloud” and has an icon with a cloud and a sun.