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**Targeted Intraoperative Radiotherapy United States (TARGIT-US)
Phase IV Registry Trial:**

A Registry Trial of Targeted Intraoperative Radiation Therapy
Following Breast-conserving Surgery

Version 9.0

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SECTION 1: BACKGROUND

1.1 Accelerated Partial Breast Irradiation in Breast Conserving Therapy:

Over the past 30 years there has been a dramatic change in the local management of breast cancer. Radical mastectomy has been replaced by more conservative surgical procedures utilizing radiotherapy in conjunction with a wide local excision of the primary tumor. Breast conservation surgery has been supported by randomized clinical trials that clearly demonstrate its equivalence to the more radical procedures with regards to local control.¹ In spite of surgical therapy moving towards “conservation”, the current standard approach continues to be radical with regards to radiotherapy fields which treat virtually all the tissues previously excised by mastectomy. A recent paradigm shift now argues for avoiding unnecessary treatment to the whole breast and limiting radiotherapy to only a portion of the breast where the primary tumor was located, i.e. partial breast irradiation.

Trials that have included lumpectomy alone as a treatment arm have documented local recurrence rates of about 40%, which is reduced by a factor of two-thirds with the addition of whole breast irradiation. The use of 45-50 Gy to the whole breast with or without a tumor bed boost achieves similar survivals as mastectomy with preservation of the breast, and achieves excellent or good cosmesis in the majority of patients. In the patients with local recurrence after irradiation, mastectomy has been demonstrated to be highly effective salvage therapy. While some patients do not have local recurrence with wide excision alone, no specific subset of patients with invasive cancer has been identified that does not benefit from breast radiotherapy in terms of local recurrence risk reduction. The randomized trials of lumpectomy alone versus lumpectomy with breast irradiation show a reduction of 63-91% in local recurrence risk with radiation. The Joint Center for Radiation Therapy conducted a trial in an attempt to identify patients with very limited cancer distribution who could be treated with wide excision alone and achieve similar outcomes as with breast irradiation.² A highly selected cohort of women with stage T1 (<2 cm) invasive cancers, resected with wide margins of > 1 cm and with no nodal involvement or lymphatic invasion were enrolled and treated with surgery alone. The overall local recurrence rate was 23%, and in patients with grade 3 tumors was 50%, therefore the local recurrence risk exceeded that expected with radiation, even in this very favorable subset. In the CALGB C9343 randomized trial for women over 70 with favorable tumor biology, 636 women were randomized to post-lumpectomy tamoxifen alone compared to tamoxifen and whole breast irradiation.³ Even in this very low risk population, the 10 year local recurrence rate was 2% with radiation and 9% without radiation.

The rationale for whole breast irradiation is based on the Halstedian principle of treating the entire breast, either through surgical extirpation or whole breast irradiation. Pathologic studies of mastectomy specimens have documented rates of multicentricity (tumor present in more than one quadrant of the breast) in breast cancer from 10-75%,^{4,5} indicating the need for treatment beyond the region of the breast involved with gross disease. Holland et al. examined mastectomy specimens with fine serial sections. In this series, 39% of specimens had no cancer beyond the index lesion, 20% had cancer confined to 2 cm beyond the index lesion, and 41% had residual cancer more than 2 cm from the index lesion⁶. Detailed examination of mastectomy specimens by Vaidya et al have shown small additional invasive or in situ cancer foci in over 60% of patients, and in fact, 80% of these are located away from the index quadrant.⁷ The concept of partial breast irradiation is based on the long-standing observation that in large studies

of breast conserving therapy, the majority of early in-breast recurrences occur near the site of the original primary tumor. This is true whether or not radiotherapy is given and whether or not the margins are involved. At 15 years after treatment, about half of all local recurrences occur in or near the original tumor, and half occur elsewhere in the breast.⁸ The rate of these “elsewhere” failures increases over time, becoming a larger percentage of the total number of local failures after longer periods of follow-up, and are likely to represent new breast cancers. The rate of elsewhere failures is similar with or without whole breast irradiation. Whole breast irradiation therefore does not necessarily prevent second ipsilateral primary cancers. This suggests that occult cancer foci away from the index lesion do not generally give rise to local recurrence, unlike that which is developed from cells surrounding the primary tumor. Given these facts, numerous institutional studies have been reported using partial breast irradiation to the tumor bed alone, without whole breast irradiation, and several randomized trials comparing standard radiotherapy to partial breast irradiation are ongoing.⁹

There are a variety of methods for delivering partial breast irradiation. The only method reported on to date with outcome data at 5 years or more involves interstitial breast brachytherapy. This method uses interstitial catheters placed in the breast either at the time of lumpectomy or at a later date. Newer methods of delivering partial breast irradiation include balloon intracavitary brachytherapy, in which a catheter and inflatable balloon are placed into the tumor bed and a high dose rate source delivers the prescribed dose to the periphery of the balloon. Also being investigated are partial breast external beam irradiation techniques which use multiple noncoplanar beams to target the tumor bed and margin based on 3D computer reconstruction with or without intensity modulated radiation therapy (IMRT). Proton beam therapy can also be used to deliver partial breast treatment allowing more precisely localized dose deposition and selective normal tissue sparing. Intraoperative radiotherapy is an emerging technique to provide a single fraction to the vicinity of the tumor bed.

There are historical randomized trials comparing APBI to standard whole breast irradiation. The Yorkshire Breast Cancer Group and Christie Hospital trials, both of which showed unacceptably high local recurrence rates with APBI, used staging, surgical and radiotherapy techniques that are not comparable to current standards, therefore their results are not applicable today.^{10,11} The other published randomized trial of APBI versus standard BCT was conducted at the National Institute of Oncology in Hungary.¹² This trial enrolled 258 patients to receive partial breast high dose rate brachytherapy (4.33-5.2 Gy x 7) to the tumor bed alone using an interstitial implant technique versus standard whole breast irradiation. At a median follow-up of 66 months, the 5 year local recurrence was 4.7% with APBI and 3.4% with whole breast radiation, and the axillary recurrence rate was <2% in both arms.

There are several institutional series from the United States that have reported outcomes after accelerated partial breast irradiation (APBI) employing LDR or HDR interstitial breast brachytherapy. The Oschner Clinic reported a case control series including 51 patients treated with either LDR (45 Gy over 4 days) or HDR (8 Gy x 9 over 4 days) interstitial breast brachytherapy, and 94 case controls treated with standard whole breast irradiation.¹³ At a median follow-up of about 75 months in both groups, local recurrence was 8% after APBI compared to 5% after standard radiation, regional nodal recurrence was 6% versus 0%, respectively, cosmesis was excellent or good in 75% versus 84%, respectively, and grade 3 complications were noted in 8% versus 5%, respectively. William Beaumont Hospital conducted a one-to-one matched pair analysis of 174 patients treated with LDR (50 Gy over 96 hours) or

HDR (4 Gy x 8 or 3.4 Gy x 10 twice daily) interstitial brachytherapy, compared to matched cases treated with standard whole breast irradiation.¹⁴ At a relatively short median follow-up of 36 months for both groups, locoregional failure was 2% after APBI versus 1% after standard BCT, and overall, disease-free and cause-specific survivals were all similar between the two groups. Fat necrosis was seen in 8% after APBI and 4% after standard BCT. A multi-institutional phase I-II study of HDR interstitial APBI also delivering 3.4 Gy x 10 in twice daily fractions reported 6% 5 year local recurrence at a follow-up of 70 months.¹⁵ Fat necrosis was noted in 28%, and excellent or good cosmesis was found in 88%. Few factors that predict the risk of local recurrence or complications are yet available from these studies, as events to date with limited follow-up have been rare.

The Radiation Therapy Oncology Group (RTOG) conducted a phase I-II study of APBI using LDR (45 Gy in 3-5 days) or HDR (3.4 Gy x 10 twice daily).¹⁶ The study which enrolled 99 women closed in 2000. Outcome data from this trial showed a 5 year actuarial rate of breast local recurrence of 4%, and regional recurrence of 3%. The American Society of Breast Surgeons (ASBS) has published their 5 year outcomes from a registry trial for the Mammosite® system. This study registered 1449 cases of Mammosite-based APBI, and noted an in-breast recurrence rate of 3.8%, identifying risk factors of negative estrogen receptor status, young age and positive margins¹⁷

The experience with partial breast irradiation in invasive breast cancer managed with breast conserving surgery (BCS) using this technique is receiving confirmation worldwide (**Table 1**).

Table 1.

Author	Patients n	IORT device and dose	Local Recurrence Rate (median follow-up)	Long term Toxicity
Luini et al ¹⁸	101	ELIOT: 70 cases single dose 21 Gy	2.0% (42 months)	1% severe fibrosis 15% mild fibrosis 4% Liponecrosis
Veronesi U et al ¹⁹	1822	ELIOT- single dose of 21 Gy	2.3% (36 months)	0.5% severe fibrosis 1.8% fibrosis, 4.2% Liponecrosis
Lemanski et al ²⁰	42	Saturne linac- single dose 21 Gy	4.7% (30 months)	No Grade 3 fibrosis 9.5% Grade 2 fibrosis
Vaidya et al ²¹	1721	Intrabeam- single dose 20 Gy	3.3% (5 year actuarial)	Grade 3-4 toxicity: 3.3%

Since 1999, the European Institute of Oncology (EIO) in Milan has conducted a randomized trial comparing intraoperative radiotherapy with electrons (ELIOT) single dose with traditional external radiotherapy in patients with unifocal breast carcinoma up to 2.5 cm of diameter and treated with breast conserving surgery. The update on the results published in 2005, with 101 cases treated with ELIOT, 70 of them treated with 21 Gy, reported a 2% incidence of local recurrence after a median follow-up of 42 months, Toxicity included of severe fibrosis (1%) , mild fibrosis, (15%) and liponecrosis (4%). Liponecrosis was described as a localized collection of brown fluid with skin erythema, with no signs of infection. The EIO also reported a series of patients who either declined participation in the randomized trial or did not fulfill the eligibility criteria was published in 2010. One thousand eight hundred and twenty two patients were treated with 21 Gy dose of intraoperative radiotherapy with electrons (ELIOT) during breast conserving surgery. The mean follow-up was 26 months, with 2.4% local recurrence rate. The late toxicity was severe fibrosis in 0.5% patients and 3.2% with mild fibrosis. Liponecrosis was observed in 4.7% cases, 2-4 weeks after surgery.

The first randomized trial of partial breast irradiation using the Intrabeam system to deliver single-fraction intraoperative radiation (IORT) was recently reported. The TARGIT trial enrolled more than 3400 patients in a randomized controlled trial comparing a single fraction of IORT to the periphery of the tumor bed to conventional whole breast irradiation over 5-6 weeks, and the early outcomes compare favorably to other forms of APBI.²¹ At five years median follow-up, the Kaplan Meier estimate of local recurrence in the conserved breast was 3.3% in the targeted intraoperative radiotherapy arm and 1.3% in external beam radiotherapy (EBRT) group. For patients who received IORT at the same time as surgery, the difference between the local recurrence rate for IORT and that of EBRT is even smaller, 1.1% for EBRT and 2.1% for IORT. The number of clinically relevant complications was not different between the two arms of the study. The annual hazard rate of local recurrence also showed a peak at three years, although longer follow up is needed to rule out a second peak at a later time point. The results, while somewhat preliminary, are encouraging for the use of intraoperative APBI in the study population, which represented a fairly low risk group overall, although 10-15% of patients had some higher risk features, such as negative estrogen receptors, age less than 45 years, tumor size larger than 2 cm, high grade histology, presence of lymphovascular space invasion or 1-3 positive nodes. Continued follow-up of these patients is ongoing to ensure long-term results are reported.

Overall, while there is a significant body of phase I-III data from studies including over 5000 women worldwide looking at toxicity and short term outcomes after APBI, this radiation therapy approach is not considered standard of care for early stage breast cancer patients at this time. While randomized trials of various APBI techniques compared to standard BCT including whole breast irradiation are ongoing, it will be several years before any mature outcome data are available. Accordingly, the current National Comprehensive Cancer Network (NCCN) practice guidelines state that partial breast irradiation “should only be performed as part of a prospective clinical trial”, and that “intraoperative radiation with photons or electrons with a single fraction (targeted intra-operative radiotherapy) can be used in institutions with that expertise and experience”.²² The main advantage of APBI is significantly shortened treatment time. Potential advantages may be gained by treating smaller volumes of normal tissue, and in particular

significantly reducing the heart and lung volumes exposed to radiation. The reduction in radiation exposure will likely lead to decreased treatment-related complications in this cancer population with an expectation of significant long-term survival. The phase I-II and early phase III data strongly suggests that results of APBI when used in selected patients are comparable to standard whole breast irradiation at follow-up periods of 3 to 5 years.

As these data mature, it is extremely important to continue to offer APBI treatment as an option to women who fit the inclusion criteria of previously published studies. This should be done under an academic model and the patients should be treated and followed under an IRB-approved protocol and informed consent process. This approach ensures that appropriate eligibility, screening and work-up, and quality assurance are performed, and that toxicity and outcome data are collected prospectively and uniformly in a larger cohort of women. These are essential steps if any form of APBI is to be established as an appropriate standard of care in various early stage breast cancer populations. A single arm registry trial is the perfect strategy to continue treatment with close follow-up as the data matures. A TARGIT-US IORT registry trial can be modeled after the American Society of Breast Surgeons' Mammosite Breast Brachytherapy Registry Trial, which has been very instrumental in establishing the long term outcomes and toxicity in balloon brachytherapy-based APBI.²³ This protocol will accomplish a similar aim for targeted intraoperative APBI. The TARGIT-US IORT registry would include patients for whom randomized data have already been collected during the original TARGIT study, essentially adopting the TARGIT trial eligibility criteria, for patients with otherwise favorable features.

1.2 The Targeted Intra-operative Radiotherapy (TARGIT) Technique

The Intrabeam® Photon Radiosurgery System is a miniature electron beam-driven X-ray source which provides a point source of low energy X-rays (50 kV maximum) at the tip of a 3.2 mm diameter tube. The radiation source can be inserted into the area of interest immediately after excision of the tumor and switched on for 15-40 minutes to provide intraoperative radiotherapy accurately targeted to the tissues that are at the highest risk of local recurrence. The dosimetric characteristics and early clinical applications of this device have been well studied and this is the device which was utilized in the international TARGIT-A trial.

The Intrabeam® device is FDA approved for use in any part of the body. For breast irradiation, the radiation source is covered by a spherical applicator that is used to uniformly conform the lumpectomy cavity around the radiation source, enabling delivery of an accurately calculated dose to a prescribe depth. Surgical sutures may also be used to maintain accurate conformance of the breast tissue to the application surface. With this approach, the surgical margins are wrapped around a radiotherapy source, i.e. the target is 'conformed' to the source and avoids the need for complex imaging to define the treatment target volume. The spherical applicators range in diameter from 1.5 to 5 cm for optimal conformance to the surgical cavity. If necessary, the chest wall and skin can be protected using sterile, radio-opaque tungsten-filled silicone shields that can be cut to size on the operation table.

The X-ray source is small and lightweight and is mounted on a surgical arm and balanced for ease of delivery and support during treatment. With the use of soft X-rays, the radiation beam is rapidly attenuated as it passes through the breast tissue adjacent to the applicator. Thus, the

highest radiation dose is received by tissue nearest the primary tumor and a much lower dose at the skin, and significantly lower doses are received by more distant tissue.

The radiation received is proportional to the time the machine is switched on. The precise dose rate depends on the diameter of the applicator and the energy of the, both of which may be varied to optimize the radiation treatment. Low energy of the radiation allows for effective shielding by the sterile sheet shielding material applied around the irradiated area. In conjunction with distance, this is typically sufficient to reduce the dose below the regulatory limit for non-badged personnel outside of an unshielded operating room. Radiation workers remaining in the OR during the irradiation would typically use additional shielding such as leaded glass. Each facility would measure radiation levels inside and outside the OR, and ensure that they are below regulatory limits, as a part of routine license/registration application process.

SECTION 2: OBJECTIVES

This is a pragmatic registry trial for women with breast cancers at low risk for local recurrence who will undergo breast IORT as sole radiation therapy post-lumpectomy (for whom equivalent local control outcomes have been published from the TARGIT randomized trial of IORT versus whole breast radiation). It is recognized that some of these patients, because of unfavorable features found subsequently in the pathologic examination of the excised lesion, will still need to have external beam whole breast radiotherapy, but omitting any external beam tumor bed boost, which will have been provided by the IORT dose. Whole breast radiation was required in 15% of cases in the international TARGIT-A trial.

The objectives of this registry trial are to establish eligibility criteria based on previously published trials and studies in order to allow women who meet these criteria to receive IORT on an IRB-approved protocol and to systematically collect and assess acute and long-term toxicity and outcomes in larger cohort of patients. This will add to the general fund of knowledge regarding this form of APBI and allow further assessment of risk groups.

2.1 Primary Objectives:

To study the efficacy and toxicity of breast radiotherapy given intra-operatively as a single fraction after breast conserving surgery, with or without whole breast radiation as indicated by pathologic risk factors, in women with early stage breast cancer.

- 2.1.1 In-breast local failure and patterns of in-breast failure
- 2.1.2 Ipsilateral regional nodal failure
- 2.1.3 Toxicity and morbidity
- 2.1.4 Relapse-free survival
- 2.1.5 Overall survival

SECTION 3: TRIAL DESIGN

3.1 Core Protocol

A pragmatic registry trial has been designed and modeled after the original successful TARGIT-A protocol, to continue the use of IORT for a select population of women, and to follow

outcomes with regards to local and regional control, toxicity and morbidity. Within this pragmatic single arm registry trial is a more selective approach that may be employed in some centers for some or all patients.

Patients selected for breast conserving surgery who are considered to have a low risk of local recurrence are eligible for the registry trial once given their informed consent. Individual centers may decide on more strict inclusion criteria and management criteria than given herein. These are to be documented in advance of enrollment of any patients onto the trial by each participating center, who will submit a Treatment Policy Statement (see section 6.1 and Appendix) and all trial patients will be treated according to this pre-declared policy. Patients will be allowed to enter the trial in one of two cohorts; the rationale for each is given below. Investigators may determine in advance which data they wish to use for entry of patients from their center and stipulate this in the Treatment Policy Statement. If the center has agreed to enroll to both cohorts, the decision about which cohort needs to be made prior to enrollment, for each individual.

3.1.1 Cohort 1 — Pre-pathology Entry

This cohort allows entry of patients who have been diagnosed with early breast cancer and whose clinical stage is suitable for treating conservatively (small tumor and no gross nodal involvement). Tumors should not be more than 3.5 cm in size, as the largest IORT applicator size is 5 cm. Patient informed consent is sought and enrollment is carried out prior to the surgical removal of the tumor (lumpectomy) with IORT delivered at the time of the lumpectomy. Postoperatively, some pathologic characteristics may be found that render the subject unsuitable for ABPI due to higher risk features for local recurrence (e.g., lobular carcinoma, positive margins at first excision, lymphovascular invasion, involved axillary nodes). According to the center's treatment policy, the patient will be recommended to have a full course of whole breast external beam radiotherapy with or without re-excision. The intraoperatively delivered radiotherapy replaces the tumor bed boost in these cases. In the international TARGIT trial, the organizers were well aware that this could provide a potential bias. The surgeon performing a local excision and placing the applicator will be aware that the patient is receiving IORT. Although the surgical excision should be similar to non-IORT standards, the surgeon may (consciously or unconsciously) remove a wider margin of normal tissue. This potential bias was studied in the randomized controlled TARGIT trial and the results showed that the excised tissue was equal in both arms.

3.1.2 Cohort 2 - Contralateral breast cancer

Unfortunately most patients who require treatment for a metachronous breast cancer are excluded from entry to trials of local treatment. Later development of a contralateral breast cancer cannot be ascribed to the first breast tumor. These breast cancers are typically treated as if they were a first time occurrence.

3.2 Trial Schema

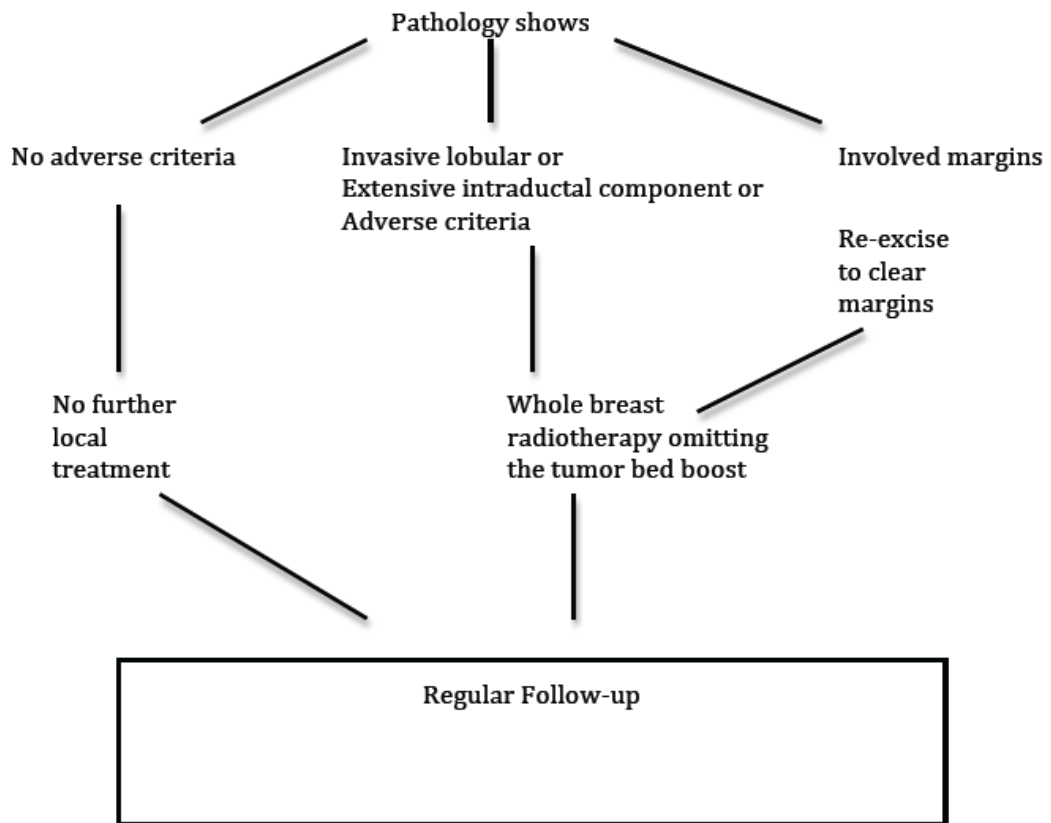
3.2.1 Trial Schema - Cohort 1 – Pre-Pathology Trial Entry

Breast cancer patient suitable for breast conserving therapy

NO RANDOMIZATION

Study Arm

Wide local excision of primary tumor
+ definitive sentinel node biopsy
+ IORT



3.2.2 Cohort 2 - Contralateral breast cancer

Patients who meet the criteria for entry into the trial but have a history of contralateral breast cancer will be eligible for entry as described in Cohort 1.

SECTION 4: ENDPOINTS

4.1 Local tumor control

Local tumor control is defined as no recurrent tumor in the ipsilateral breast. Patients will be regularly monitored as per the individual center's policy provided this meets the minimum trial criteria for follow-up with physical examination at least every 6 months for 3 years and yearly at 4 and 5 years post-treatment.

Confirmation of recurrence will follow clinical examination and cytology or biopsy. See section 7.

4.2 Site of relapse within the breast will be recorded in order to assess whether the recurrence is at the site of initial tumor or at a new site and whether it has occurred within the treated field (IORT). The trial CRFs detail how to record the site of the initial tumor and any subsequent breast recurrence.

4.3 Local toxicity and morbidity will be recorded as adverse events related to the primary treatment of the breast cancer. These were recorded in the randomized trial and outcomes showed no significant difference in clinical complications for the IORT as compared to standard external beam radiation. However, all expected toxicities of hematoma, seroma, wound infection, wound breakdown and delayed wound healing will be assessed according to RTOG criteria. Late skin reactions, rash, telangiectasia and pain due to radiation and all other toxicities will be recorded and graded according to standard NCI-CTCAE V. 4 criteria (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

4.4 Relapse-free survival will be recorded as the time interval between trial entry and the date of confirmation of any recurrence. The actual date to be used is the clinic day on which the investigations that led to a confirmed diagnosis of the recurrence were requested. Relapse-free survival would include any recurrence of breast cancer (local, regional or distant) or death without prior report a relapse. All patients will be analyzed under an "Intent to Treat" policy.

4.5 Overall survival will be the time interval between enrollment and death.

SECTION 5: SELECTION and ENTRY of PATIENTS

5.1 Eligible patients: Cohorts 1 and 2

- Female

- Age 45 years old or older with operable invasive breast cancer
- T1 and T2 (<3.5 cm), N0, M0, confirmed by clinical, cytological or histological examination
- Suitable for breast conserving surgery and radiotherapy
- Ipsilateral diagnostic mammogram within 12 months of enrollment

Those with previously diagnosed and treated contralateral breast cancer may be entered. It is recommended that patients meet an ECOG performance status of 0-3, however, grade 4 patients can be treated at the discretion of the participating center.

Individual centers may wish to restrict entry to a more exactly defined subset of patients in which case only patients with these characteristics may be entered by the particular center. For example, centers may decide at outset to recruit only women over the age of 50 or possibly only postmenopausal women. Such policies must be predefined in writing on the Treatment Policy Statement form, submitted and approved by the Steering Committee, and followed for all patients enrolled at that center. See section 6.1.

Before entering any patient into the trial, the local investigator should confirm that the patient would be available for regular follow-up for at least 5 years.

5.2 Exclusion criteria

5.2.1 All Cohorts:

- Age < 45 years
- Known axillary lymph node positive breast cancer (FNA not required)
- Invasive lobular cancer
- Tumor size > 3.5 cm
- Multicentric cancer in the same breast as diagnosed by clinical examination, mammography, ultrasound, MRI or pathologic assessment, not amenable to excision with negative margins with a single lumpectomy.
- Synchronous bilateral breast cancer at the time of diagnosis.
- Ipsilateral breast had a previous cancer and/or prior in-field radiation.
- Patients known to have BRCA1/2 gene mutations (testing for gene mutations is *not* required).
- Patients undergoing primary systemic treatment (hormones or chemotherapy) as initial treatment with neoadjuvant intent of reducing tumor size.
 - Patients who undergo a short course of anti-estrogen therapy (2-4 weeks) are NOT to be excluded because there is no neoadjuvant intent of reducing tumor size
- Previous history of malignant disease does not preclude entry if the expectation of relapse-free survival at 10 years is 75% or greater
- Any factor included as exclusion criteria in the participating center's Treatment Policy Statement.

5.3 Patient entry to the trial

Patients will be entered to the trial only after being given full information about the trial included in a written information sheet. Each patient should be given time to consider participation and ask questions before giving consent by signing the patient informed consent form. A patient deemed suitable for the trial will only be allowed enrollment once informed consent has been freely and voluntarily given. Once eligibility is confirmed and the informed consent form is signed, a patient will be enrolled into the trial and assigned a trial number.

If a patient chooses to withdraw, she can write a letter to the site PI or coordinator center PI expressing his or her desire to withdraw from the trial and provide a dated signature.

5.3.1 Cohort 1 – Pre-pathology Entry

Those patients who will have intraoperative radiation therapy at the time of primary surgery will be enrolled in the cohort after giving consent but prior to the planned surgery.

5.3.2 Cohort 2 - Contralateral Entry

If the patient has a previous contralateral breast cancer then they will be entered as a separate stratum, with their other eligibility for cohort 1 as determined appropriate.

5.3.3 Patient Consent

Sample consent forms are provided by the Steering Committee and may be modified to meet institutional criteria, but all changes must be approved by the Institutional Review Board, as well as by the Steering Committee prior to enrollment of any subjects onto the registry.

SECTION 6: TREATMENTS

6.1 Treatment Policy Statements

Prior to entry of any patients each participating center will register with the Steering Committee and complete a Treatment Policy Statement which has been approved by the Steering Committee. The Treatment Policy Statement will define the categories of subjects to be entered in each cohort and details of the treatment policy (e.g. fractionation and dose of whole breast radiotherapy to be used). The Steering Committee must be notified in writing prior to implementation of any change to practice during the course of the trial, in order to audit the patients entered and to confirm that treatment remains true to the core protocol.

Only clinical centers with the Intrabeam® device or those who are able to refer patients to such a center may participate in this trial. Centers with newly acquired equipment must consult the trial operation center prior to entering patients into the trial. The quality control of the Intrabeam system set up must be confirmed by the Coordinating Center before enrollment of patients can begin.

6.2 Surgery

All patients will have local excision of the primary tumor following appropriate clinical workup. No specific assessments prior to enrollment will be required although mammography and

ultrasound are strongly recommended to facilitate identification and exclusion of multi-focal disease and to determine as accurately as possible the size of the tumor.

Surgery will be according to practice standards at each participating center. Complete macroscopic excision of the tumor is required. The aim of the local excision should be to achieve the widest margin of excision while maintaining a good cosmetic outcome. For superficial tumors, an ellipse of overlying skin can be excised. The depth of resection will depend on the position of the tumor within the breast and the size of the breast, but in most instances will extend to the pectoral fascia.

In all patients, but especially in those women with non-palpable tumors where pre-operative localization has been performed, the specimen should be well oriented with sutures or clips according to local protocols and x-rayed intraoperatively. The specimen x-ray should be examined in the operating room to ensure complete excision of the lesion and to assess the adequacy of the margins. Further tissue should be taken from a margin if intraoperative assessment indicates that tumor extends near the margin. Specimens must be processed in order to allow pathologic assessment microscopically of all margin widths.

Either a standard sentinel node biopsy or at least a level I axillary node dissection with removal of at least 6 axillary lymph nodes must be performed in all patients. Wound closure must be performed meticulously (air and water-tight) and sutures (if non-absorbable) should remain in place for 14 days.

6.2.1 Cohort 1: Pre-pathology Stratum

6.2.1.1 Patients with Positive Margins

If final pathology shows involved or close margins (evidence of invasive or in-situ tumor at or within 1 mm of an excision margin), re-excision is strongly recommended, however, final margin width will be dependent on participating center's institutional policy and will be stated in the Treatment Policy. In some cases margin status may necessitate a mastectomy. If re-excision is not performed and the margin width does not meet that which is required by the Treatment Policy, the subject is no longer eligible for IORT alone, and should be treated with whole breast irradiation, omitting the external beam boost. For subjects enrolled pre-pathology who have already received IORT, re-excision to negative margins must be followed by external beam radiotherapy with exclusion of a boost, or undergo mastectomy.

6.2.1.2 Patients with High Risk Features

Subjects selected for IORT alone whose surgical pathology specimens reveal higher risk with the following pathologic features:

- Axillary lymph node positive breast cancer
- Invasive lobular cancer
- Tumor size > 3.5 cm
- Extensive Intraductal Component (EIC= $\geq 25\%$ of the lumpectomy specimen involved with ductal carcinoma in situ, DCIS) as assessed on surgical pathologic lumpectomy specimen.

- Multicentric cancer in the same breast as diagnosed by pathologic assessment, not amenable to excision with negative margins with a single lumpectomy.
- Inability to assess pathologic margin status
- Any factor included as exclusion criteria in the participating center's Treatment Policy Statement.

These subjects must be advised to receive external beam whole breast radiotherapy, since these subjects are at a higher risk of developing a local or regional recurrence, therefore are rendered unsuitable for IORT alone. External beam radiotherapy will be administered in addition to the IORT that they have already received, and should not be followed by an external beam tumor bed boost. These subjects should remain in the trial should continue to be followed according to the original enrollment cohort as per protocol.

Alternatively, a mastectomy may be performed based on the histopathology findings, multidisciplinary consultation, or patient preference. The indication for mastectomy must be recorded on the patient's trial case report form. The patient should remain in the trial should continue to be followed according to the protocol. If mastectomy is performed, the use of post-mastectomy irradiation will be at the discretion of the radiation oncologist.

6.2.1.3 Patients who do not receive IORT

A patient will no longer be followed and will be "Off Study" if he/she was not given IORT during surgery or was deemed clinically ineligible for IORT by the site investigators after signing consent. No data needs to be reported for this patient.

6.2.2 Cohort 2: Contralateral

Patients should be managed as described for Cohort 1 as indicated by their risk features.

6.3 Pathological Examination

Data from the pathological examination should be recorded on the appropriate data collection forms in accordance with the T N M classification. Failure to assess and record all required pathologic criteria will necessitate pathologic re-review to achieve complete pathologic classification or this could result in protocol violation.

6.4 Radiotherapy

The technique of the operation and the delivery of radiotherapy has been described and published previously. An instructional video produced by Carl Zeiss is also available from the Steering Committee. All participating centers must be trained and submit required radiation quality assurance data according to Section 11.2.

6.4.1 Preparation of the Intrabeam

Intraoperative radiotherapy will be delivered in the operating room immediately after the removal of the tumor. All patients should receive a prophylactic dose of antibiotic just before skin incision. The device and the arm of the stand are wrapped in a sterile clear plastic cover. The individual applicators are sterilized prior to the surgery session.

The size of the applicator sphere is determined at surgery by the surgeon and/or the radiation oncologist. An appropriately sized in applicator fits comfortably without tension but allowing conformation of the surrounding tissue, and so that the skin and some subcutaneous tissues can be gathered with purse string suture over the sphere. Any other apparatus to assist this apposition may also be used.

It is essential to achieve complete hemostasis before insertion of the applicator sphere, because even a small amount of bleeding can distort the cavity around the sphere and significantly reduce the radiation dose to adjacent breast tissue. The applicator sphere is inserted into the surgical cavity and pursestrings suture may be inserted in the breast tissue to bring together the target breast tissue so that it conforms well to the surface of the spherical applicators and is held in place during treatment. The skin, but not the breast tissue, should be retracted away from the radiation source device using surgical sutures to prevent direct contact with the applicator. It is important to keep the skin at a distance of at least 1cm from the applicator surface.

If necessary, sterile protective tungsten sheets used according to the manufacturer's instructions may be applied by the surgeon to protect deep structures (heart and lung) if the deep margin of the excision is at the chest wall. The skin flap may also be protected by placement of moistened gauze between the skin and applicator shaft. Regardless of the shielding utilized, care must be taken to avoid inadvertent shielding of tissue that requires radiation treatment.

6.4.2 IORT dose prescription and delivery

The surgeon and radiation oncologist should choose the largest possible suitable applicator in order to ensure the optimal dose is delivered to the tumor bed tissue.

The protocol allows for one dose prescription. A dose of 20 Gy at the surface of the applicator is prescribed by the radiation oncologist and delivered to the breast tissue. This takes approximately between 15-40 minutes depending on the size of the applicator.

During the radiation treatment, the anesthesiologist, clinician and physicist may remain within or adjacent to the operating room. To avoid unnecessary exposure of hospital personnel, it is recommended that as many people as possible vacate the operating room and those remaining either wear a lead apron or remain behind a shielded screen.

6.4.3 Completion of IORT

After completion of radiation the conforming sutures are removed. Strict hemostasis should be obtained following the removal of the Intrabeam device. The skin is sutured meticulously to achieve a watertight closure as per the surgeon's usual technique.

6.4.4 External beam irradiation

External beam techniques will be used uniformly in all patients who require whole breast irradiation regardless of the cohort into which they were enrolled. It is recommended that the RTOG breast contouring atlas guidelines should be followed when target and normal tissue

volumes are contoured and dose-volumes evaluated. A linear accelerator with a minimum energy of 6 MV should be used for treatments.

Whole breast irradiation should be delivered to the entire ipsilateral clinical breast volume with an adequate margin (1.5 to 2 cm) and appropriate compensation to keep the maximum dose less than 15% above prescription dose. A dose of 45 to 50.4 Gy in 1.8 to 2 Gy per fraction, or 42.56 Gy in 2.66 Gy per fraction may be used. Dose calculations should use homogeneity corrections. It is strongly recommended that three dimensional CT-based treatment planning be used in all cases. The lumpectomy cavity should be contoured on the planning CT and the treatment fields should cover this volume with adequate dose (at least 95% of the prescribed dose). Intensity modulated radiotherapy (IMRT) is usually not appropriate for intact breast irradiation, but may be used in conjunction with appropriate image guidance if it provides a substantial reduction in normal tissue (heart or lung) doses, or significantly improved dose homogeneity in the target volume.

No external beam boost should be delivered, as all patients will have already received an IORT boost.

The following dose constraint guidelines as per ongoing RTOG breast trials are recommended:

Tumor bed: 100% to receive \geq 95% prescribed dose

Ipsilateral lung: < 15% to receive 30% prescribed dose

Contralateral lung: < 15% to receive 5% prescribed dose

Heart (left sided tumor): <5% to receive 40% prescribed dose

Heart (right sided tumor): <5% to receive 5% prescribed dose

If the subject is not receiving chemotherapy, then whole breast irradiation should start within 9 weeks of the final surgical procedure. If the subject is to receive chemotherapy, then the radiation should begin within 6 weeks of the final dose of chemotherapy, not including trastuzumab or other biologic systemic therapies, or hormonal therapies, which may be administered concurrently with breast irradiation.

6.5 Adjuvant Systemic Therapy

Following completion of intraoperative radiation therapy, patients may be advised to receive adjuvant systemic therapy according to local practice. The sequencing of adjuvant therapies is not governed by this protocol, but careful consideration should be given to the timing of chemotherapy in patients who are scheduled to receive external beam radiotherapy after intraoperative therapy

SECTION 7: PATIENT FOLLOW-UP and RECORDING of EVENTS

7.1 Follow-up and Notification of Recurrence, Adverse Events, and Death

Patients should be followed according to local guidelines and these should be noted on the policy statement prior to entry into the trial. However, submission of case report forms will be required for each patient at six-month intervals for the first three years and yearly for years four and five. Each patient should be seen within a six-week window of the planned visit date according to the

follow-up calendar. At each visit the patient should be offered a physical examination and asked whether she has experienced any adverse events. Below is a list of suggested patient interactions.

<u>Visit 1</u>	<u>Visit 2</u>	<u>Visit 3</u>	<u>Visit 4</u>	<u>Visit 5</u>	<u>Visit 6</u>	<u>Visit 7</u>	<u>Visit 8</u>	<u>Visit 9</u>	<u>Visit 10</u>	<u>Visit 11</u>
Initial screening by surgeon	Rad-onc consult to consent patient and discuss trial and radiation therapy.	Six-week follow up with Surgeon	6 mo f/u. Breast exam and/ or mammo	1-year f/u. Breast exam and/ or mammo	1.5-year f/u. Breast exam and/ or mammo	2-year f/u. Breast exam and/ or mammo	2.5-year f/u. Breast exam and/ or mammo	3-year f/u. Breast exam and/ or mammo	4-year f/u. Breast exam and/ or mammo	5-year f/u. Breast exam and/ or mammo

It is recommended that mammography of the ipsilateral breast occur at six month intervals post-treatment for the ipsilateral breast for the first three years then yearly thereafter. Any other radiological examination is at the discretion of the local clinicians.

For patients enrolled on the new contract starting 9/15/2017, submission of follow-up case report forms will only be required for the second and fifth year follow-up. The initial case report form is required as usual.

Patient follow-up may extend beyond the 5 year follow-up period specified in this protocol. An optional 10 year follow-up telephone questionnaire may be added as a sub-protocol and patients will be consented to be contacted at this later time point.

7.2 Recording of Recurrence Events

Local recurrence includes any ipsilateral invasive or non-invasive breast tumor recurrence. Location of local recurrence, for the purpose of this protocol, is defined as “true” recurrence in the index quadrant of the breast versus “elsewhere” if in another quadrant of the ipsilateral breast. Regional recurrence is defined as recurrence in the ipsilateral axillary, infraclavicular, supraclavicular or internal mammary lymph nodes.

Confirmation of ipsilateral recurrence must be by histology or unequivocal cytology. Clinical examination and imaging are not sufficient. Careful recording of the site of the recurrence is required to determine whether it is at the site of the original tumor and/or within the treatment field to determine whether the disease is true or elsewhere.

Recurrence at any other site, including contralateral breast or contralateral regional nodes, must be confirmed by appropriate imaging and/or biopsy. Details of both first local or regional and first distant recurrence are required to be submitted as well as the status of the patient with regard to active disease when treatment for local disease has been completed.

Development of recurrence or new malignancy, including in the contralateral breast, must be reported on the case report forms once a diagnosis has been confirmed.

7.3 Guidelines for the Management of Recurrence

The management of recurrent disease will be left to the discretion of the participating institution. If appropriate, patients having had intraoperative radiation therapy alone are able to have conventional radiation as part of the management of a recurrence, according to institutional standards.

7.4 Adverse Events

For purposes of this study, only those adverse events (AEs) related to the surgery or radiation will be reported, as this study includes no guidelines or requirements regarding any systemic therapy. Patients on this trial will be assessed for acute and late radiation morbidity, according to NCI CTCAE criteria, version 4. Adverse events may be recorded at any time following the surgery for the 5 year observation period.

7.4.1 Adverse Event Reporting Requirements

7.4.1.1 Expected Adverse Events

Expected adverse events are adverse reactions or events that are thought to be related to the research procedure. For the purpose of this trial the following is a list of potential expected AEs.

- Fibrosis
- Wound complication
- Wound infection
- Wound dehiscence
- Hematoma in breast or axilla
- Seroma
- Dermatitis radiation
- Telangiectasia
- Pain in the radiated field
- Localized edema in the breast

Expected AEs will be recorded in the complication form and will be completed per Standard Operating Procedure manual.

7.4.1.2

Unexpected adverse reactions are adverse reactions or events that are thought to be related to the research procedure but do not appear on the list as mentioned above. These are recorded in the complication form if grade 3 or more according to CTCAE criteria. Unexpected AEs should also be reported to the coordinating center within 5 days of being brought to the attention of the investigator and reported to the site's Institutional Review Board per its requirements.

7.4.2 Serious Adverse Events (SAEs)

A serious adverse event is defined as any event that is fatal, life-threatening, causes or prolongs hospitalization, causes disability or incapacity, or requires medical intervention to prevent permanent impairment or damage,

7.4.3 Serious Adverse Events Reporting Requirements

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Only SAEs related to surgery or radiation need to be reported to the coordinating center. These related SAEs must be reported directly to the coordinating center as soon as possible and at least within five working days of the investigator becoming aware of the adverse event. An early report can then be followed up by a more detailed report.

All serious adverse events that occurred during the period of observation must be documented on the serious adverse event form and complication form. Any complications following surgery with intraoperative radiation therapy must be reported on the complication form. It is also the investigator's responsibility to report them to the local institutional IRB as required by local regulations.

The clinical course of the serious adverse event should be managed according to accepted standards of medical practice until a satisfactory explanation is found or the investigator considers it medically justified to terminate follow-up of this event. Should the adverse event result in death, a full pathological report should be supplied if possible.

7.4.4 Period of Observation

For the purpose of this trial, the period of serious adverse event observation extends from the time of registration onto the trial until 5 years after the completion of the intraoperative radiation therapy. Trial follow up should continue according to schedule once the SAE is resolved.

7.5 Deaths

All deaths with date and cause must be reported as soon as possible to the coordinating center on the appropriate case report form. Deaths which also meet SAE criteria should additionally be reported as described in 7.4.3.

7.6 Withdrawal of Consent

Patients may opt out of the trial at any time by signing a letter of intent to withdraw. At this point, the patient will be censored and no further data will be collected. Such cases should be reported to the coordinating center immediately so that no further data are entered onto the database.

SECTION 8: DATA OWNERSHIP and PUBLICATION

The management of this trial is the responsibility of the Steering Committee, which also owns the rights to all data collected on the trial. Individual centers own the rights to the data collected on patients entered from their own center. However, by agreeing to participate in this trial, investigators also must agree not to present or publish any analysis of their institutional data on trial patients until after the first publication of the overall result for the whole trial. The policy for publication of the trial has been agreed by the Steering Committee.

The Steering Committee will meet regularly and review all matters of trial conduct and will also address any questions relating to the trial. Responsibility for any decisions on the management

of the trial and its publications is invested in the clinical and scientific academic members of the committee.

8.1 Trial Administration

Since this is a multicenter trial, it has been agreed that each center takes responsibility for the collection and management of its own data. Any other arrangement requires approval by the Steering Committee. Each participating center will be required to provide names of staff completing case report forms, and confirming that the staff has completed Good Clinical Practice training. In addition, each site coordinator must complete a data entry training webinar with the coordinating center. The data will be entered into an electronic CRF system, which every coordinator will gain access to only after completing the required training. A major component of this training is to streamline data entry and prevent the submission of inaccurate and incomplete data.

Each participating center must submit the required data forms and case report forms to the coordinating data center within required time limits. The Steering Committee will monitor and have access to all the data. Regular electronic reports will be produced and passed to each center for audit and monitoring purposes.

Data submission from each site will be monitored closely by the coordinating center. The first five patients from each site will have all CRF's verified by coordinating center. Depending on the results of this initial data audit, a minimum of 20% of all CRF's will be audited for the duration of the study.

The following source documents are required to be uploaded to verify CRF data. Please note, all documents should be redacted of patient names and medical record numbers, and should have their TARGiT-US study identifier only. These processes will be included in the required data training session.

1. Clinic note, which includes documentation of eligibility including patient age, size of tumor by clinical or imaging evaluation, and confirmation of invasive cancer suitable for breast-conserving surgery.
2. Surgical Pathology report(s) for all surgical procedures, including the IORT procedure
3. Post-surgery clinic note documenting adjuvant therapy, complications, recurrences, or any other significant events in the follow-up period (only included if applicable)

Participating sites will be reimbursed for each patient entered onto the trial, but only after confirmation that the required CRF's have been validated for accuracy and completeness. The following table outlines the case report forms required in order to receive reimbursement:

Reimbursement Schedule for Participating Centers

Date	Item	Amount
Year 1: Annual patient recruitment payments	Accrual payments: Patient reimbursement payments due upon verification of completion of the following: <input type="checkbox"/> Uploaded Consent	\$500 per patient

	<input type="checkbox"/> Eligibility Criteria <input type="checkbox"/> Demographic Information <input type="checkbox"/> On Study Information <input type="checkbox"/> Treatment Information <input type="checkbox"/> Serious Adverse Event Form(s) (if applicable) <input type="checkbox"/> Entry Form <input type="checkbox"/> Surgery Form <input type="checkbox"/> Pathology Form <input type="checkbox"/> IORT Form <input type="checkbox"/> EBRT Form (if applicable) <input type="checkbox"/> Adjuvant Therapy Form <input type="checkbox"/> Additional Procedure Form (if applicable) <input type="checkbox"/> Complication Form(s) <input type="checkbox"/> Follow-up Forms (1 month, 6 months, and 1 year) Concomitant medications Forms (Day 1, 1 month, 6 months, and 1 year)	
End of year 3: Annual patient reimbursement payments for follow-up	<p>Follow-up payments: Patient reimbursement payments due upon verification of completion of the following Case Report Forms:</p> <input type="checkbox"/> Follow-up Forms (1.5 years, 2 years, 2.5 years, 3 years) <input type="checkbox"/> Serious Adverse Event Form(s) (if applicable) <input type="checkbox"/> Complication Form(s) (if applicable) <input type="checkbox"/> Concomitant medications Forms (1.5 years, 2 years, 2.5 years, 3 years) <input type="checkbox"/> Local/Distance Recurrence Forms (if applicable)	\$300 per patient
End of year 5: Annual patient reimbursement payments for follow-up	<p>Follow-up payments: Patient reimbursement payments due upon verification of completion of the following Case Report Forms:</p> <input type="checkbox"/> Follow-up Forms (4 years, 5 years) <input type="checkbox"/> Serious Adverse Event Form(s) (if applicable) <input type="checkbox"/> Complication Form(s) (if applicable) <input type="checkbox"/> Concomitant medications Forms (4 years, 5 years) <input type="checkbox"/> Local/Distance Recurrence Forms (if applicable)	\$200 per patient
	Total:	\$1000 per patient

NOTE: Collaborating sites will not be reimbursed for patients enrolled on the new 9/15/2017 contract.

Any data management or clinical queries should be addressed in the first instance to the principal investigator at the local center. If the investigator cannot adequately address the question it should be passed to the coordinating center, which will either deal with the query directly or pass it on to the Steering Committee.

In addition to the initial data audits, ongoing data quality monitoring, with appropriate feedback to each participating center, will be conducted by the coordinating center at six-month intervals under the oversight of the Steering Committee. Participating centers who do not abide by the Standard Operating Procedures and Good Clinical Practice guidelines will have patient reimbursement withheld and their continued participation will be at the discretion of the Steering Committee. Data monitoring reports will be reviewed by the Steering Committee as outlined in Section 11.3.

SECTION 9: STATISTICAL CONSIDERATIONS

9.1 Patient Numbers and Power Calculations

The objective of this trial is to enroll patients in a single arm protocol and monitor local tumor control.

The sample size calculation for the TARGIT US Registry Trial (a prospective observational cohort study with no comparator group) assumes a background rate for local recurrence and utilizes the following calculation.

If λ_0 = background rate

δ is the difference between background rate and current recurrence rate

For a given level of α and β , the sample size is calculated using method by Machin et al²⁴:

$$n = \frac{[z_{1-\alpha}\sqrt{\lambda_0} + z_{1-\beta}\sqrt{(\lambda_0 + \delta)}]^2}{\delta^2}$$

For TARGIT US Registry trial, the background recurrence rate is assumed to be 4.5% and the current rate of recurrence is set at 2.00%. Delta is the difference between background rate and current recurrence rate. Sample size has been calculated using the following: Alpha=5% and Power=90%, resulting in a required 755 patients. An excess of 5% will be added as a rule for anticipated ineligible subjects, increasing the total sample size to 793. The two patient cohorts will not be separated for the analysis regarding local control.

Background Rate	Current Rate	Delta	Alpha	Power	Sample size
4.50%	2.00%	0.025	5%	90%	755

The original international TARGIT trial was written as a non-inferiority trial. Its recent publication in the Lancet shows that the intraoperative radiation therapy is not inferior to standard external beam radiation therapy at a median follow-up of four years. As that data continues to mature, this registry trial will enroll patients for the purpose of both verifying those results and collecting additional outcome and toxicity data.

ASTRO, the governing body for radiation oncology, recently changed their guidelines for IORT. Although the published data has been promising, the group's recommendation is that IORT with lower-energy X-ray should only be used for prospective registry trials. In order to continue offering this radiation treatment in accordance with the ASTRO guidelines the accrual has been increased to 1500 patients. In discussion with the other collaborating sites on the study, we've expressed a mutual desire to continue the study in order to continue offering IORT and to continue looking at toxicity data, local recurrence numbers, etc.

9.1.1 Early Stopping

Early stopping of this trial is within the power of the Steering Committee. Reasons for early stopping include:

- Any grade V toxicity
- More than 5 grade IV toxicities within the first 50 patients reported at the 6 month follow-up
- More than 10 grade IV toxicities within the first 100 patients reported at the 6 month follow-up
- More than 5% local recurrences after the first safety report
- Skin breakdown and wound dehiscence (reported at 6 weeks of after procedure), which after detailed review of the Steering Committee as to time course and severity, were considered clinically significant

There will be one formal interim analysis for efficacy of this single arm therapy once half the expected number of patients has been enrolled or once half of the expected events has occurred, whichever happens first. If at this time local recurrence is noted to be significantly different then the parent TARGIT trial (outside the initial 2.5% non-inferiority boundary; in which local recurrence is more than 5%) then early stopping will be undertaken.

9.1.2 Additional Sub-protocols

Additional sub-protocols will be written to address questions such as quality of life, patient preference, and health economics. Each sub-protocol will have its own statistical considerations and will be funded independently of this protocol.

9.2 Statistical Analysis

The major endpoint is the incidence of local recurrence. This will be calculated on the basis of intention-to-treat. All three cohorts will be combined for the local recurrence analysis.

In addition, exploratory subgroup analyses will be performed on the main endpoint including variables such as timing of IORT with respect to surgery, tumor size, grade and axillary node involvement.

SECTION 10: ETHICAL CONSIDERATIONS

This registry trial uses a well-established technology with FDA approval to deliver intraoperative radiation therapy. The recent results of the analysis with four years median follow-up showed that the TARGIT is equal in efficacy as compared to external beam radiation therapy for selected patients. Although the median follow-up is less than five years, the annual hazard rates are very promising with a peak incidence of local recurrence at 3 years. This is supported by other large randomized trials, which show a similar peak incidence of local recurrence within the first 2-3 years. However, these results should be interpreted with caution and the Intrabeam technology for delivering radiation therapy whether as sole therapy or as a boost should continue to be monitored within a well-organized clinical trial. Until sufficient follow-up time has elapsed to establish this modality as an alternative standard of care and the appropriate patient selection determined. All suitable patients will be informed of the trial and given the opportunity to participate. Patients will be given a period of time to consider entry and to complete the consent form. Entry into the trial will only proceed once signed consent form has been received at the clinic.

SECTION 11: QUALITY ASSURANCE

11.1 Quality Assurance Procedures:

All the evidence to date supports the description of the Intrabeam as delivering an accurate and reliable dose. Physicists on site at each participating center are responsible for verifying the miniature x-ray source is operational prior to use and setting up the parameters within the control console software for treatment delivery. During the procedure, the control console monitors the system for safe and accurate dose delivery.

The Intrabeam System includes a full set of quality assurance tools. These combined with the operator interface of the control console allow complete verification of all of the performance functions in minutes and constant monitoring of critical treatment parameters throughout the treatment. The participating centers are responsible for Q/A according to the manufacturer's instructions detailed in the User Manual and these data must be submitted to the coordinating center.

The set of dosimetric QA procedures described in the User Manual is at its core a set of relative calibration verification tests based on the absolute calibration performed at the factory. Each participating site shall submit documentation about the site's device for review before enrolling patients in the study. This documentation will include ion chamber calibration certificate, independent absolute dose measurement for the bare probe showing agreement with 5% of the factory measured value (in which the charge measured and all of the factors used to convert the reading to absolute dose should be included; a measurement at a distance of 2cm is recommended), description of the depth dose measurement setup, factory measured depth doses for the bare probe and each applicator, Analysis of site measured depth dose showing agreement within 5% of the factory measured depth dose for at least 1 applicator, where the depths measured should range from the closest possible distance to the applicator to at least 2cm from the surface of the applicator. This should be done at acceptance, annually, and following major repairs/replacement of the accelerator unit.

Recalibration of the output of the X-ray source must be performed at least annually and a report must be submitted to the coordinating center. Carl Zeiss-Meditec, Inc. offers contracts for annual manufacturer service. For quality assurance purposes, the operations office will request from each site annually or after every 50th patient (whichever is earlier) a printout of the system parameters.

11.2 IORT Physics and Quality Assurance

Prior to entering any patient into the trial, participating centers will submit data for each X-ray source probe and applicator set in use. Each participating center will be responsible for measuring data for the probe and applicator set and shall submit the data supplied by the manufacturer for comparison with measured data together with a copy of the letter of acceptance supplied by Carl Zeiss-Meditec, Inc. In the event that a new applicator that has demonstrated equal effectiveness is developed, it can be used in this protocol. The same information for the applicator must be collected as described below. Information regarding the new applicator must be submitted to the IRB as a minor modification to the protocol.

In addition, if a center was not previously a member of the international TARGIT randomized controlled trial, it is strongly suggested that five pilot cases be performed prior to enrollment of any study subjects (followed by an audit by a member of the steering committee), a case be proctored on site by a surgeon designated by the Steering Committee, or investigators attend TARGIT Academy (a training program covering all aspects of the TARGIT technique) to ensure that the investigators and medical team is familiar with the device. Dose prescription and planning protocols for the conventional radiotherapy will vary among centers, but for each center, the Treatment Policy Statement approved by the Steering Committee must specify the techniques that will be used for all enrolled subjects. All patients that receive whole breast external beam radiotherapy in addition to intraoperative radiation therapy must be treated in accordance with this policy.

The following will be collected for each treatment delivered: applicator serial number, applicator size, prescribed dose, treatment time, kilovolts and microamps.

11.3 Data and Safety Monitoring

The Steering Committee will be responsible for both data and safety monitoring oversight. All data collected for this trial is compliant with Good Clinical Practice guidelines, as outlined by the IHC-GCP guidelines. The data monitoring process will be conducted by the coordinating center. Each participating center must submit the required documentation and complete the required training and certification process prior to entering any subjects on study. Each participating center must submit all required documentation on all enrolled subjects during the five-year follow-up period. Ongoing data quality monitoring, with appropriate feedback to each participating center, will be conducted by the coordinating center at six-month intervals under the oversight of the Steering Committee. Each participating center may be required to undergo a monitoring site visit as needed.

Currently there is an independent, international Data Safety Monitoring Committee for the International TARGIT-A Trial. All patient safety concerns from the International Trial will be

communicated directly to the TARGIT-US Steering Committee, and any early stopping will be implemented simultaneously in both the U.S. and international trials. The TARGIT-US coordinating center will conduct six-month evaluations of complication rates and local recurrence rates for the entire cohort. If safety issues are identified from either a single institution or multiple institutions, the U.S. Steering Committee will take appropriate action.

SECTION 12: REFERENCES

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