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[redacted]

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[redacted] STUDY SYNOPSIS

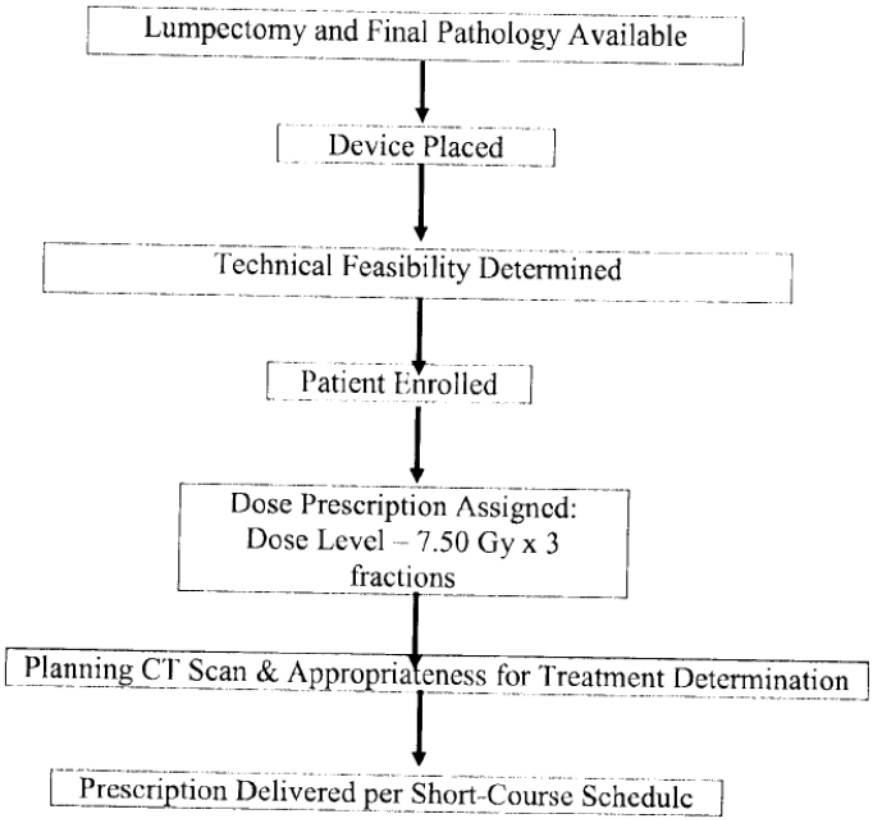
1.1 Study Design

This multiple site, prospective, non-randomized study has been designed to characterize the toxicity of delivering accelerated partial breast irradiation (APBI) in a short course, 2-3 day fashion. In our previous trial, we demonstrated the safety of such an approach. (NCI/Clinicaltrials.gov identifier: NCT01019720).

The schema below is a summary of the study design. Although we used a 3 fraction dose of 8.25 Gy/fraction in our earlier study, we now will use a dose of 7.50 Gy based on guidance from the NSABP Breast Cancer Steering Committee, to test a schedule consistent with 50 Gy in 2 Gy fractions. A minimum of 6 hours must occur between dose fractions. We will allow treatment to be delivered with 1) multicatheter interstitial implant or 2) SAVI (Cianna) or Contura MLB (Hologic) applicators.

Data collected during this study will include baseline patient demographics, information related radiation therapy treatment delivery, toxicities, cosmetic outcomes and recurrence data. The patient's follow-up data will be collected during the patient's standard follow-up visits.

1.2 Study Schema



1.3 Study Objectives

1.3.1 Primary Objectives

To determine the toxicity rate with shorter courses of APBI delivered with a breast brachytherapy applicator.

1.3.2 Secondary Objectives

1.3.2.1 To determine the 3-year actuarial local control rate with abbreviated APBI.

1.3.2.2 To assess the rate of excellent or good cosmesis at 2-years after shorter courses of APBI and to identify co-variants associated with and predictive of poor cosmetic outcome in women treated with an overnight treatment course of APBI.

1.4 Study Endpoints

1.4.1 Primary Endpoint

The treatment will be considered unsafe if a 2-year serious toxicity rate exceeding 10% cannot be excluded with the 95% interval. Serious toxicity in this study is defined as toxicity greater than grade 2 using CTCAE v4.0 criteria. In a cohort of 200 patients, there should be 11 or fewer serious toxicities to exclude a rate of 10% using the upper limit of the 95% confidence interval.

1.4.2 Secondary Endpoints

1.4.2.1 We will assess 3- year estimates of local control using the Kaplan-Meier method. We expect the estimated 3-year local control rate to be greater than 95% (corresponding to a 3-year local failure rate of 5% or lower).

1.4.2.2 The percentage of patients with good/excellent cosmetic results at 2-years should exceed 80%.

1.5 Study Population

200 women with early stage breast cancer (TIS, T1-2, N0) removed with breast conserving surgery achieving a negative pathologic margin may be enrolled.

1.5.1 Inclusion Criteria

1.5.1.1 Must sign informed consent

1.5.1.2 Female age 45 or older at diagnosis

1.5.1.3 Surgical treatment of the breast must have been lumpectomy. The margins of the resected specimen must be histologically free of tumor (negative surgical margins per NSABP criteria).

1.5.1.4 On histologic examination, the tumor must be DCIS and/or invasive breast carcinoma.

1.5.1.5 For patients with invasive breast cancer, an axillary staging procedure must be performed [either SNB alone or axillary dissection (with a minimum of six axillary nodes removed), and the axillary node(s) must be pathologically negative]. Patients > 70 with ER+ tumors no greater than 2 cm do not require axillary evaluation, but MUST be clinically node negative on examination and all available imaging (clinical N0).

1.5.1.6 The T stage must be Tis, T1, or T2. If T2, the tumor must be ≤ 3.0 cm in maximum diameter.

1.5.1.7 Estrogen receptor positive tumor and/or progesterone receptor positive tumor (not applicable to DCIS).

1.5.2 Exclusion Criteria

1.5.2.1 Age < 45 at diagnosis (regardless of histology)

1.5.2.2 Pregnant or breast-feeding

1.5.2.3 Active collagen-vascular disease (patients not on medication AND ESR<20 AND CPK in normal range are eligible for study)

1.5.2.4 Paget's disease of the breast

1.5.2.5 Prior history of DCIS or invasive breast cancer

1.5.2.6 Prior breast or thoracic RT for any condition

1.5.2.7 Multicentric carcinoma (DCIS or invasive)

1.5.2.8 Synchronous bilateral invasive or non-invasive breast cancer

1.5.2.9 Surgical margins that cannot be microscopically assessed or that are positive

1.5.2.10 Positive axillary node(s)

1.5.2.11 T stage of T2 with the tumor > 3 cm in maximum diameter or a T stage ≥ 3

1.5.2.12 Estrogen receptor negative and progesterone receptor negative tumor

1.5.2.13 If any of the dosimetric treatment criteria as defined in Section 9.7 have not been met. Patients who become ineligible due to inability to meet dosimetric criteria should not receive treatment as defined in this protocol and will come off the study. Any subsequent adjuvant radiation will be delivered at the discretion of the treating physician.

2. INTRODUCTION

2.1 Clinical Background

The equivalence of breast conserving therapy (BCT) to mastectomy has been established in multiple prospective randomized trials[1-5]. Despite the obvious cosmetic and potential emotional advantages of BCS+RT, many patients may choose mastectomy or lumpectomy alone over BCS+RT due to the protracted course of daily treatment involved with WBI, which consists of daily radiotherapy to the whole breast for 25 treatments usually followed by a boost to the tumor bed, delivered over the course of 6-6.5 weeks. Other reasons which may steer women away from BCS+RT have been identified as physician bias, patient age, fear of radiation treatments, distance from a radiation treatment facility, and socioeconomic factors[6-8].

In response, accelerated partial breast irradiation (APBI) has been studied increasingly over the past 15 years as a viable alternative to WBI. In general, APBI involves treating the surgical cavity with a 1-2 cm margin, thus reducing the volume of breast tissue by up to 50% using various radiotherapeutic methods. Technical approaches of APBI include multi-catheter

interstitial brachytherapy, balloon catheter brachytherapy, external 3-D conformal external beam radiotherapy (3D-CRT) and intra-operative radiotherapy (IORT). Treatment is typically delivered post-operatively, over a short period of time, using large fraction sizes. Advocates of APBI state that it is a safe, well tolerated therapy that allows for equivalent cosmetic outcomes while significantly increasing quality of life and allowing for an effective treatment of the patients' breast cancer. To date, pilot studies of various APBI techniques have been studied and large, multi-center randomized controlled studies are underway comparing APBI to WBI.

2.2 Rationale for Accelerated Partial Breast Irradiation

In standard BCT, radiotherapy is delivered to the whole breast to eliminate areas of occult multi-centric in-situ or invasive carcinoma. Additional radiotherapy may be delivered to the tumor bed using a 'boost' to eliminate the higher burden of microscopic disease that may have been left in close proximity to the tumor bed after lumpectomy.

The fact that a majority of true local relapses occur in close proximity to the tumor bed, along with available pathologic data demonstrating a low likelihood of microscopic tumor burden more than 1-2 cm beyond the primary tumor, provides rationale for more localized treatment in selected patients[9-11]. With APBI, a conformal dose of radiation is delivered to a limited volume of breast in a short period of time. Currently, there are several ongoing phase III trials addressing this issue using various APBI techniques. In the United States, an intergroup trial (National Surgical Adjuvant Breast and Bowel Project B 39 & Radiation Therapy Oncology Group 0413) is randomizing patients with early stage breast cancer to WBI versus APBI.

2.3 Data Supporting Partial Breast Irradiation

Currently available literature describing the safety and efficacy of APBI can be divided into 3 main groups by the method of treatment delivery. The three predominant methods with available data include multi-catheter interstitial brachytherapy implants, single-catheter balloon brachytherapy implant, and 3-D conformal external beam-based treatment delivery. The data supporting and describing the first two methods will be summarized briefly.

Interstitial brachytherapy using multiple catheters was the first method by which APBI was accomplished. The William Beaumont Hospital group has the largest experience using interstitial brachytherapy with the longest reported follow-up of 199 patients with early stage breast cancer[12]. Eighty percent of these patients were treated on institutional protocols with the following criteria: invasive ductal histology, tumor size < 3.0 cm, negative margins (≥2 mm), age > 40 years, and negative lymph nodes. The other 20% were treated with APBI for 'compassionate' reasons and included patients with close margins, DCIS, participation in other studies, and timing of radiotherapy after lumpectomy. The median age was 65 years and 12% of patients had 1-3 positive lymph nodes. One hundred twenty patients were treated with LDR brachytherapy, receiving 50 Gy over 96 hours while the rest of the cohort underwent HDR brachytherapy, receiving either 32 Gy in 8 fractions or 34 Gy over 10 fractions. The target volume included the lumpectomy cavity with a 1-2 cm margin for all patients. The group also included a matched pair analysis to compare the rate of local recurrence between APBI and WBI. At 60 months, they reported a 1% local recurrence rate in both the APBI and WBI groups. There was also no difference in distant metastases, disease free survival, cause-specific survival, or overall survival between the two groups. Furthermore, in patients with 60-month follow-up,

99% of patients reported their cosmesis to be good or excellent. Ten-year data were recently reported by the Beaumont group with no significant changes in the rates of local recurrence in the breast compared to WBI.

The MammoSite® RTS (Hologic) breast brachytherapy balloon device was designed to treat a similar volume around the lumpectomy cavity compared to interstitial brachytherapy but with a single skin entry point. The device received FDA clearance in May 2002, and provides a simpler, less user-dependent method of APBI[13]. Since the US Food and Drug Administration (FDA) approved the original single-lumen MammoSite RTS (Hologic), the use of brachytherapy is believed to have increased dramatically. A study of Medicare billing claims among women treated with BCT estimated that the use of brachytherapy as a component of oncologic care increased in incidence from less than 1% of cases in 2001 to 10% of cases by 2006[14]. The American Society of Breast Surgeons has enrolled and followed a cohort of 1,440 women treated with the single-lumen MammoSite catheter on a registry trial. This group has reported a 5-year actuarial IBTR rate of 3.8%[15]. Of the patients in this study, 90.6% had good-to-excellent cosmesis, 13% developed symptomatic seromas, 9.5% developed an infection, and 2.3% developed fat necrosis, results comparable to those seen with MIB[16].

More recent multiple-lumen devices allow greater flexibility in treatment planning, enabling both better coverage of the target tissue at risk and decreased dose to the nearby structures such as rib and skin[17,18]. The Contura™ MLB (SenoRx, Irvine, CA) brachytherapy balloon device is a second-generation single-entry applicator that adds 4 additional lumens, offset by 5 mm, to the central channel. Similarly, the SAVI applicator (Cianna Medical, Aliso Viejo, CA) also has multiple strut-adjusted lumens allowing greater dose optimization than single lumen devices[18].

2.4 The Challenge Posed by IORT

Intraoperative radiotherapy

While APBI has enjoyed acceptance by way of professional society endorsement for certain patients, the utility and appropriate use of single-fraction radiotherapy as a method of APBI remains contentious and undefined. There are three major causes for concern with current IORT methods: 1) Patients are selected for a treatment strategy without full pathological review of data, 2) dose to the target volume is not consistent with known radiobiology, and 3) the treating physicians are unable to graphically evaluate and monitor doses delivered to the target volule or the normal tissues. Worryingly, recent updates of the two seminal randomized trials of IORT completed in Europe are demonstrating results that are inferior to both whole breast irradiation and fractionated APBI.

The TARGIT approach employs an intraoperative spherical applicator to deliver a single dose of 20 Gy at the applicator surface with 50 kV x-rays, which results in a dose of 5 Gy at 1 cm. Due to the physical constraints imposed by this technology, a higher dose at depth would create an unacceptably high dose at the surface of the applicator and the breast tissue in contact. Initial findings of the TARGIT-A trial were published prematurely in *Lancet*[19]; a total of 2232 women were randomized to either fractionated whole breast radiotherapy (with or without a boost) or to targeted intraoperative radiotherapy at a dose of 20 Gy at the applicator surface. Patients were grouped into two strata: the prepathology stratum included patients who had their first definitive lumpectomy and TARGIT at the same sitting, while the postpathology stratum

consisted of patients who were taken *back* to the OR for the TARGIT treatment after final pathology had been reviewed. Notably, 21% of patients in the pre-pathology stratum were triaged for additional, "remedial" whole breast irradiation on account of unfavorable pathological features[20]. Patients on the post-pathology stratum were selected for TARGIT after pathological review and did not receive whole breast irradiation. In the initial publication, no difference was seen in local recurrence rates in the two randomized groups. In the updated results presented recently, a total of 3451 patients were randomized and followed for a median of 2 years and 5 months[21]. The 5-year ipsilateral breast recurrence rate is higher in the TARGIT-treated patients, 3.3% vs 1.3%, p=0.042. The 5-year rate of ipsilateral breast recurrence in the post-pathology stratum (ie well-selected patients, none of whom required "remedial" whole breast RT) was surprisingly high at 5.4% (compared to 1.7% for whole breast RT).

The dose delivered by TARGIT is (at least based on our current understanding) inadequate for the control of microscopic disease, even after correcting for the RBE of a 50 kV beam. Confusingly, the same dose of 20 Gy at the applicator surface (5 Gy at depth) is used for partial breast monotherapy treatment and as a "boost" in the event of "remedial" whole breast irradiation. This creates an irreconcilable situation; either the monotherapy dose is too little or the combined treatment is too much. The toxicity event rate was very low in the TARGIT A trial, indicating that the combined treatment dose is probably not excessive. Current results appear to confirm that the monotherapy dose is, unsurprisingly, too modest to be efficacious.

The Milan group, led by Vernonesi and Orrechia, has simultaneously studied a different technology for the same purpose: intraoperative radiotherapy with electrons (ELIOT). In the ELIOT technique, the breast margins are re-apposed intraoperatively and an intra-operative dose of 21 Gy is prescribed to the 90% isodose line with 3-12 MeV electrons. In the most recent update of the ELIOT trial, 1305 were randomized, 654 to the whole breast arm and 651 to the ELIOT arm[22]. With a median follow-up of approximately 6 years, the 5-year ipsilateral breast tumor recurrence rate was 4.4% in the ELIOT arm and 0.4% in the whole breast arm (p<0.0001). The corresponding 5-year "true" local recurrence rates were 2.5 vs 0.4% (p=0.0003). Significantly higher rates of fat necrosis were seen with ELIOT (14% vs 7%, p=0.04)

With the ELIOT approach, a homogenous dose is delivered to a target volume that is generally consistent with the target volumes treated in the accumulated APBI literature. However, the ELIOT approach is agnostic to final pathology findings; no "remedial" treatment is offered to women found to have positive margins or positive lymph nodes. The impact of positive margins on local failure is well documented. Margin-status from the primary lumpectomy specimens is not reported in the ELIOT data; however approximately 25% of patients in both groups were node-positive, with approximately 5% with pN2a disease (>3 positive nodes). The ELIOT results amply highlight the perils of poor patient selection that may come with intraoperative radiotherapy. Furthermore, the clinical fat necrosis rate in the ELIOT patients on the randomized trial was much higher (14%) than the 2.3% reported with balloon-device based APBI. This is almost certainly because the 21 Gy dose was arrived at using linear-quadratic formalism and an incorrect a/B ratio of 10 for breast cancer. While acknowledging the imperfection of linear-quadratic assumptions at doses above 8-12 Gy, the ELIOT dose is almost double the 2 Gy equivalent-dose of fractionated courses of APBI. Thus the ELIOT experience as reported in the interim results of the randomized trial is fraught with not one but two major reasons for pessimism—suboptimal tumor control and higher toxicity.

However, given that the IORT trials are large randomized trials, an important outstanding question for APBI is "Can the the APBI schedule be similarly shortened?". Efforts at compressing the fractionation of applicator-based APBI to a 2-day treatment course have been reported from the William Beaumont Hospital and a collaborative multi-institutional effort reported earlier by our group[23,24]. The Beaumont group reported on a cohort of 45 patients treated with 4 fractions of 7 Gy over 2 days. With a median followup of 3.7 years and a minimum follow-up of 2 years, only grade 1 and 2 toxicities were reported. The most common toxicities were: fat necrosis (18%) and asymptomatic seroma (42%). Three patients had rib fractures. In our first report of the "schedule seeking" Overnight Trial, we reported on 30 women treated on the first cohort of 7 Gy x 4 fractions. No grade 3 toxicities were noted; one breast infection, and 2 each cases of fat necrosis and symptomatic seromas were seen.

2.5 Fractionation Schemes

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

Effect = E = n(ad + bd2) where

d = dose/fraction

n = # identical fractions

Estimates of the α/β ratio for squamous cell carcinomas of the head, neck and cervix uteri are > 7 Gy. For this reason, the α/β ratio for tumor control probability is taken to be 10 Gy by convention, while the α/β ratio for normal tissue effects is taken to be 3 Gy. Different fractionation schemes can be equated using the relationship:

(nd/n1d1) = (a/b + d1)/(a/b + d) where

n = standard number of fractions

n1 = equivalent number of fractions in altered schedule

d = standard dose/fraction

d1 = desired dose/fraction

Although relatively high cumulative doses of radiation are needed for tumor control, the daily fraction size has to be respectful of the fraction sensitivity of normal tissues in the treated volume. Accounting for these assumptions, increases in fraction size have to be compensated for by reductions in cumulative radiation dose, which typically are insufficient for tumor control. As a result, daily fractions of 1.8-2 Gy are delivered over 4-8 weeks to reach a cumulative dose of 45-80 Gy.

The above discussion ignores the potential effect of cellular proliferation that may occur during a

course of radiation therapy. Although commonly ignored because of the uncertainty of the relevant variables, a correction can be introduced into the above equation for this factor[25]:

$BED = nd\,[1+d/\alpha/\beta-[(\ln 2)T\ /\ (\alpha)Tpot]$

BED = biological effective dose

d = dose/fraction

n = # of identical fractions

T = overall treatment time after initial time lag to proliferation

Tpot = potential tumor doubling time

Rosenstein et al. in their publication comparing several APBI fractionation schemes used a Tpot value of 13 days, an initial time lag of 14 days, and an α/β value of 0.3.

In contrast to the assumptions for most epithelial tumors, the α/β ratio for breast tumors may be much lower than the conventional assumption of 10 Gy. In vitro experiments in human breast carcinoma cell lines have suggested an α/β ratio of about 4 Gy. An interesting set of clinical dose-response data for inoperable and locally recurrent breast cancer was published in 1952[26], and reanalyzed to fit the linear-quadratic model[27]. The point estimate for the α/β ratio from this data set was 4-5 Gy. Based on this data set, the Royal Marsden Hospital and the Gloucestershire Oncology Centre collaborated in a randomized clinical trial to evaluate the relative toxicity and efficacy of different fractionation schemes[28,29]. A total of 1410 women were randomized to one of three arms:

1. 50 Gy in 25 fractions over 5 weeks
2. 39 Gy in 13 fractions (3.0 Gy/fx) over 5 weeks
3. 42.9 Gy in 13 fractions (3.3 Gy/fx) over 5 weeks

The overall treatment time was kept constant in all three arms. In the experimental arms, 5 fractions were delivered over 2 weeks. All patients were treated in the supine position. The primary endpoint was late breast change. Local control was a secondary endpoint. The 39 Gy arm was less likely to develop late radiation change compared to both 42.9 Gy and 50 Gy, but also had worse local control than the 42.9 Gy arm. The α/β ratio for any late breast change was 3.6 Gy and the α/β ratio for tumor control was 4 Gy. The similarity of these two estimates is striking and serves to validate the hypofractionated regimens commonly being used for APBI. To summarize, although the true α/β ratio for breast cancer remains unknown, the most robust clinical data set seems to suggest an α/β ratio of 4 Gy.

In APBI, the most commonly used fractionation schemes include 340 cGy delivered in a twice-daily administration, and 385 cGy delivered twice a day. The NSABP B-39/RTOG 0413, endorses both of these fraction sizes.

2.6 Rationale of Proposed Fractionation Scheme

The primary rationale for APBI is the enhanced convenience for patients which may result in increased access to BCT. The fractionation schemes for APBI were devised largely empirically. With data now available documenting the low α/β ratio for breast cancer, the fraction sensitivity

of breast cancer can be further exploited with higher fraction sizes, resulting in even more compressed treatment times. However, care must be taken to not exceed the tolerance of normal tissues. The reference schedule that will serve as our standard is 50 Gy delivered in 2 Gy fractions. This is partially based on guidance we have received from the NSABP Breast Steering Committee, where an expert panel recommended 50 Gy in 25 fractions as the reference schedule (whole breast RT without boost). This schedule is appropriate for the low risk patients such as those scheduled for APBI and is consistent with NSABP-B39/RTOG0413.

Assuming tumor parameters: $\alpha/\beta = 4$ Gy; $\alpha = 0.27$ Gy^{-1}, if repopulation effects are neglected, reference schedule of 50 Gy/25 fractions delivers a tumor BED of 75 Gy_4. Wyatt et al. [30] have reviewed postoperative repopulation parameters relevant to breast cancer and used working values of: effective doubling time $T_{eff} = 26$ days; delay time = 0 days. This yields a K factor of $0.693 / (\alpha \times T_{eff}) = 0.693 / (0.27 \times 26) = 0.1$ Gyday^{-1}.

A 25 fraction treatment normally lasts around 32 days, thus the calculated BED is reduced by $32 \times 0.1 = 3.2$ Gy, i.e., the reference tumor BED, corrected for repopulation, is 75 Gy4 – 3.2 ~ 72 Gy_4. Note that these assumptions lead to a tumor BED of 71.8 Gy_4 for a 50 Gy/25 schedule.

For the APBI treatment, assume the balloon is spherical with an average diameter of 4.5 cm. Dose is prescribed 1cm from the balloon surface, i.e., the balloon radius is 2.25 cm and the prescription distance is 3.25 cm. Between the balloon surface and the dose prescription surface there is a large dose gradient. Assuming an inverse-square relationship, the dose on the balloon surface is greater by a factor of $(3.25/2.25)^2 = 1.44$, i.e., the surface dose is 44% higher than the prescription dose.

The radiobiological influence of the dose gradient may be accounted for using the analytical principles discussed in the method described by Dale et al[31]. This approach calculates a Multiplying Factor (MF) with which to multiply the prescribed BED (BEDprescribed) in order to take account of the dose gradient effect, the radiosensitivity parameters, the fractional dose and the number of fractions. The resultant BED (BEDactual) is that of the equivalent uniform dose which would produce the same cell kill as the reference schedule.

The table below summarizes those results which give the closest match (in 0.25 Gy increments) to the reference BED for a 3 fraction schedule of balloon treatments.

Dose/Fraction (Gy)	MF	BEDprescribed (Gy_4)	BEDactual (Gy_4)
3 Fraction Treatment (brachytherapy)			
7.25	1.16	61.0	70.8
7.50	1.15	64.5	74.3

The methodology on which the above calculations are based assumes uniform density of tumor cells between the balloon surface and the reference surface. If the cellular density decreases with distance away from the balloon surface (as is likely) then that is an advantage since the fractional cell kill will be greater than predicted.

Given the above calculations, we propose to treat our protocol patients with 3 fractions of 7.50 Gy using either multicatheter implants or a multilumen brachytherapy device or a hybrid implant of the two approaches. External beam will not be allowed on this study.

Of note, a similar fractionation scheme is found in the HDR treatment of prostate cancer, where 4 fractions of 9.5 Gy are delivered twice daily over 2 days, with an overnight stay[32]. This HDR fractionation scheme has toxicities which are comparable or improved compared to LDR prostate brachytherapy. The prostate is a glandular organ with a reportedly low α/β ratio, similar to the breast.

2.7 Contura Multi-lumen Balloon and SAVI strut-adjusted applicator

See Appendix 2 for detailed figures of the device and Appendix 3 for the device inserts which includes description and use.

3. STUDY DESIGN

This multiple site, prospective, non-randomized phase II study has been designed to determine the safety of delivering APBI with a brachytherapy applicator in a short course, 2-3 day fashion.

Data collected during this study will include baseline patient demographics, information related radiation therapy treatment delivery, toxicities, cosmetic outcomes and recurrence data. The patient's follow-up data will be collected during the patient's standard follow-up visits. All patients will be asked to return for clinic visits for a minimum of 2 years. The investigator will continue to review and collect data from the patient's medical record for disease status until the study is completed. This information will be collected to help in data analysis for the secondary objective and resolve any queries that may arise during data analysis and for publication.

3.1 Participating Institutions

Arizona Breast Cancer Specialists (Scottsdale, AZ), William Beaumont Hospital Radiation Oncology (Royal Oak, MI), Bryn Mawr Hospital Cancer Center (Bryn Mawr, PA), University of California San Diego Health System (La Jolla, CA), and 21st Century Oncology of Michigan (Farmington Hills, MI), Huntsman Cancer Hospital, University of Utah (Salt Lake City, Utah), Cedars Sinai Medical Center (Los Angeles, CA), Cleveland Clinic (Cleveland, OH).

3.2 Duration of Study

The duration of the study will be 6 years. Three years to ensure sufficient patient accrual, an additional 2 years for follow up and data analysis.

4. STUDY OBJECTIVES

4.1 Primary Objective

To determine the toxicity rate with shorter courses of APBI delivered with a breast brachytherapy applicator.

4.2 Secondary Objectives

4.2.1.1 To determine the 3-year actuarial local control rate with abbreviated APBI.

4.2.1.2 To assess the rate of excellent or good cosmesis at 2-years after shorter courses of APBI and to identify co-variants associated with and predictive of poor cosmetic outcome in women treated with an overnight treatment course of APBI.

5. STUDY ENDPOINTS

5.1.1 Primary Endpoint

The treatment will be considered unsafe if a 2-year serious toxicity rate exceeding 10% cannot be excluded with the 95% interval. Serious toxicity in this study is defined as toxicity greater than grade 2 using CTCAE v4.0 criteria. In a cohort of 200 patients, there should be 11 or fewer serious toxicities to exclude a rate of 10% using the upper limit of the 95% confidence interval.

5.1.2 Secondary Endpoints

5.1.2.1 We expect that estimated 3-year local control rate (using Kaplan-Meier method) should be greater than 95% (corresponding to a 3-year local failure rate of 5% or lower). We will assess 3- year estimates of local control using the Kaplan-Meier method.

5.1.2.2 The percentage of patients with good/excellent cosmetic results at 2-years should exceed 80%.

5.1.3 Cosmesis

The percentage of patients with good/excellent cosmetic results at 2-years should exceed 80%.

6. STUDY POPULATION

200 women with early stage breast cancer (TIS, T1-2, N0) removed with breast conserving surgery achieving a negative pathologic margin may be enrolled.

6.1 Inclusion Criteria

6.1.1 Must sign informed consent

6.1.2 Female age 45 or older at diagnosis

6.1.3 Surgical treatment of the breast must have been lumpectomy. The margins of the resected specimen must be histologically free of tumor (negative surgical margins per NSABP criteria).

6.1.4 On histologic examination, the tumor must be DCIS and/or invasive breast carcinoma.

6.1.5 For patients with invasive breast cancer, an axillary staging procedure must be performed [either SNB alone or axillary dissection (with a minimum of six axillary nodes removed), and the axillary node(s) must be pathologically negative]. Patients $\geq$ 70 with ER+ tumors no greater than 2 cm do not require axillary evaluation, but MUST be clinically node negative on examination and all available imaging (clinical N0).

6.1.6 The T stage must be Tis, T1, or T2. If T2, the tumor must be $\leq$ 3.0 cm in maximum diameter.

6.1.7 Estrogen receptor positive tumor and/or progesterone receptor positive tumor (not applicable to DCIS).

6.2 Exclusion Criteria

6.2.1 Age < 45 at diagnosis (regardless of histology)

6.2.2 Pregnant or breast-feeding

6.2.3 Active collagen-vascular disease (patients not on medication AND ESR<20 AND CPK in normal range are eligible for study)

6.2.4 Paget's disease of the breast

6.2.5 Prior history of DCIS or invasive breast cancer

6.2.6 Prior breast or thoracic RT for any condition

6.2.7 Multicentric carcinoma (DCIS or invasive)

6.2.8 Synchronous bilateral invasive or non-invasive breast cancer

6.2.9 Surgical margins that cannot be microscopically assessed or that are positive

6.2.10 Positive axillary node(s)

6.2.11 T stage of T2 with the tumor > 3 cm in maximum diameter or a T stage $\geq$ 3

6.2.12 Estrogen receptor negative and progesterone receptor negative tumor

6.2.13 Any of the dosimetric treatment criteria as defined in Section 9.7 have not been met. Patients who become ineligible due to inability to meet dosimetric criteria should not receive treatment as defined in this protocol and will come off the study; any subsequent adjuvant radiation will be delivered at the discretion of the treating physician.

7. STUDY SCHEDULE

7.1 Screening and Enrollment

Prior to enrollment in the study, potential participants will be evaluated to determine eligibility. The patient will have undergone standard lumpectomy surgery to remove the tumor. The surgery must have provided negative surgical margins using the NSABP definition.

The investigator will explain the study purpose, procedures, and patient responsibilities to the potential participant. The participant's willingness and ability to meet the follow up requirements will be evaluated. Written informed consent will be obtained from all potential study patients prior to participation.

To register eligible patients on this study, each site will contact Rutgers Cancer Institute of New Jersey's OHRS Registration Desk (732) 235-8990 and fax (732) 235-9399 the signed and dated eligibility checklist, completed signature page of the consent form and additional source documents if requested by OHRS. Once the OHRS Registration Desk verifies eligibility and properly executed consent, a unique patient study number will be issued. The patient will not be identified by name. This is the point that the patient is considered on study. **Patients will not start protocol treatment prior to registration.**

7.2 Applicator Placement

The applicator will be placed using ultrasound guidance. Applicator refers to any device used to deliver brachytherapy on this study, including individual 6F catheters, the SAVI applicator, and the Contura MLB applicator. The balloon of the Contura MLB is inflated with a saline/contrast mixture (maximum of 2-3% contrast) to fill the cavity. The balloon will remain inflated throughout the duration of the radiation and will be removed after the last fraction. The SAVI device will be deployed fully using the turn-style and will remain open until the last fraction, when it can be collapsed and removed. Following applicator placement, a treatment planning CT scan must be performed to evaluate the patient for skin spacing, symmetry and applicator conformance.

7.3 Treatment Planning

CT imaging is mandatory for treatment planning. Standard treatment planning guidelines for APBI will be employed. CT-based 3-D brachytherapy treatment planning will be conducted using commercially available software and equipment. The treatment will be performed using available high dose rate (HDR) brachytherapy. (Refer to Section 9 for specific details regarding dosimetric guidelines and quality assurance criteria.)

7.4 Prescription Delivery and Brachytherapy Treatment

In general, brachytherapy should start between 1-5 days after balloon placement.

Dose - 7.50 Gy X 3 = 22.5 Gy delivered in 3 fractions over 2-3 days

In addition, to confirm that the patient's position is identical to the position of the initial planning CT, the applicator's inflation status and rotational motion will be verified prior to each fraction. If any problems are found during the confirmation check, refer to the Instructions for Use (refer to Appendix 3 or the applicator package for the most recent version). All treatments will be completed using commercially available HDR and Ir-192 radioactive sources.

Note: A minimum of 6 hours must occur between dose fractions.

7.5 Applicator Removal

The applicator removal should be scheduled after completing the treatment. The applicator should be removed using standard technique and the applicator exit/entrance site should be dressed according to standard medical practice.

7.6 Post-Applicator Removal Follow-Up Visits

The patient should be seen according to the standard of care for follow-up office visits. The first post-RT office visit should occur between 2-8 weeks post-treatment, then at least annually for years 1 and 2 post- RT. (see Appendix 1). Mammography should be performed according to institutional standards of practice and is generally performed as a baseline 6-12 months after brachytherapy and repeated annually.

The occurrence of adverse events, including toxicities, second primary cancers, and deaths (on therapy or prior to evidence of disease progression), will be monitored continuously. Recurrences and new cancers detected using standard imaging will be documented. Biopsy and additional treatment will also be documented, if applicable. Cosmetic grading, seroma formation, infection, fibrosis, fat necrosis, pain, telangiectasia, must be evaluated and reported at each visit.

7.7 Study Completion

An exit case report form must be completed for all study participants.

7.7.1 Patient Completion

A patient is considered to have completed the study if the follow-up examinations were completed through year 2.

7.7.2 Patient Discontinuation

7.7.2.1 A patient may be discontinued from the study at the discretion of the investigator if the patient's condition deteriorates or if the investigator decides that continuing in the study may be detrimental to the health or welfare of the patient.

7.7.2.2 Voluntary withdrawal from the study by the patient (note: voluntary withdrawal may occur at any time during the study and will not affect the patient's future medical treatment or benefits)

7.7.3 Patient Lost to Follow-Up

A patient may be lost to follow-up for non-treatment related reasons. Reasons for loss to follow-up include, but are not limited to:

7.7.3.1 Patient has moved from the area

7.7.3.2 Patient is unwilling or unable to return for follow-up

8. Brachytherapy Applicators

8.1 Device Description

8.1.1 Applicator and Tray

Several vendors provide 6 F catheters for soft tissue implantation and any of these can be used for the purpose of a multicatheter implant. Catheters can be packaged individually or bundled and are shipped sterile by vendors or can be sterilized at the provider site. The Contura MLB and SAVI applicators are used to position tissue and radioactive sources during breast brachytherapy treatments. They each consist of a multi-lumen tube, while the Contura has an inflatable balloon assembly at its distal end and the SAVI has peripheral struts that deploy/expand. The SAVI device is available in four sizes, 2.4 (mini), 3, 4, and 5 cm diameters.

The Contura MLB is available with two balloon sizes; a variable diameter ranging from 4-5 cm or 5-6 cm. The balloon fill volumes are listed below:

4-5 cm BALLOON	
Fill Volume (cc)	Diameter (mm)
33	40
35	41
37	42
39	43
42	44
44	45
47	46
50	47
52	48
55	49
58	50

5-6 cm BALLOON			
Fill Volume (cc)	Diameter (mm)	Fill Volume (cc)	Diameter (mm)
40	40	69	51
42	41	73	52
44	42	77	53
47	43	80	54
49	44	84	55
51	45	88	56
54	46	93	57
57	47	96	58
59	48	102	59
63	49	108	60
66	50		

The applicator trays are supplied in sterile packaging and come packaged with the equipment needed to implant the applicator. The Instructions for Use and chart labels are also provided in the applicator tray.

8.1.2 Afterloader Connector Accessories

Standard adapters or transfer tubes needed to connect the applicators to the various commercially available HDR machines are available from the HDR manufacturers.

8.2 Physics Training

It is the responsibility of each participating institution to have a thorough understanding of the proper placement, management and removal of the applicators prior to study participation and that proper and effective quality assurance procedures are followed for each case. Physics training is available (by the manufacturer of the device) and is strongly recommended.

9. TREATMENT PLANNING & DOSE DELIVERY

9.1 Imaging

A treatment planning CT scan with the patient in an easily reproducible position with the applicator in place will be required for assessing appropriateness for treatment and treatment planning. The CT scan should at least include 3 cm both cephalad and caudal to the applicator for proper assessment of dose delivery. A CT scan thickness of ≤ 0.3 cm should be employed. The following structures will be contoured: (a) applicator surface, (b) planning target volume for evaluation (PTV_EVAL) – (see below), (c) trapped air and/or fluid, (d) skin surface, and (d) aspect of the closest rib that is adjacent to the balloon. The target volumes and normal tissue structures should be outlined on all CT cuts when appropriate.

It is critically important that at the time of the planning CT, the rotational orientation of the applicator is documented so that prior to each treatment the proper orientation can be reproduced. It is suggested that the shaft orientation line position be noted and a skin mark or the skin incision be used for consistent rotational positioning. Additionally, a dummy marker wire can be placed into lumen #1 to further document orientation of the device for proper CT planning or multiple dummy wires placed in each lumen for identification.

9.2 Target Volumes

As the applicator moves with the target, compensation for variability of treatment set-up and breathing motion is not needed; the planning target volume for evaluation (PTV_EVAL) = clinical target volume (CTV) = planning target volume (PTV). Therefore, within this protocol, only the PTV_EVAL will be referenced. The PTV_EVAL will be delineated as the breast tissue volume bounded by the uniform expansion of the balloon radius in all dimensions by 10 mm less the balloon volume and limited to 5 mm from the skin surface and by the posterior breast tissue extent (chest wall and pectoralis muscles are not to be included) as long as dosimetric criteria can be met.

When determining dose coverage of the PTV_EVAL to assure compliance with dose requirements, as outlined in Section 9.7, the volume of trapped air/fluid must be accounted for as it displaces a percentage of the target beyond 1 cm from the balloon surface. The area of trapped air/fluid will be contoured at each level, a total volume obtained and the percentage of the PTV_EVAL that it displaces calculated. When determining the PTV_EVAL dose coverage, this displaced percentage must be subtracted. For example, if the percentage of PTV_EVAL displaced by trapped air/fluid is calculated to be 5-10%, then to comply with criteria, the dose coverage must be at least 95% of the PTV_EVAL receiving 90% of the prescribed dose. If the percentage of PTV_EVAL displaced by trapped air/fluid is greater than 10%, then it is not possible to achieve acceptable dose coverage and the patient will not be enrolled.

9.3 Treatment Planning

Radioactive source location, number of lumens, number of positions and dwell times are at the discretion of the physician and will be determined by High Dose Rate CT-based 3D treatment planning to produce the optimal conformal plan in accordance with volume definition and dose requirements. The treatment plan used for each patient will be based on analysis of the

volumetric dose including dose-volume histogram (DVH) analyses of the PTV_EVAL and critical normal tissues.

9.4 Determination of Appropriateness for Treatment

Appropriateness for treatment will be based on the ability to achieve the dosimetric goals. However, three basic parameters can be used for determining whether the geometric placement will provide the ability to achieve the dosimetric goals. These basic parameters include: (a) tissue-device conformance, (b) device symmetry, and (c) minimal device-skin distance. As a result of the dose shaping capabilities of the SAVI and Contura MLB applicators, minimum requirements for these geometric parameters are case dependent. The general rules are outlined as follows:

9.4.1 Tissue-Device Conformance

Ideally, the lumpectomy cavity surface should be in direct contact with the entire balloon surface or with the struts of the SAVI applicator, assuring maximum prescription dose coverage of the PTV_EVAL. Frequently air and/or fluid will be identified between the lumpectomy cavity and applicator surface. Either as a result of an irregular cavity shape or because the air/fluid is trapped, a less than ideal conformance results and "pushes" a percentage of the PTV_EVAL beyond the prescription isodose line coverage. To determine the significance of the trapped air/fluid, these volumes will be contoured and used in calculating PTV dose coverage (Section 9.7). Typically, when the volume of trapped air/fluid is < 10% of the PTV, acceptable dose coverage can be achieved. No adjustment is needed if the volume is less than 5%. For displaced volumes that are 5-10% fo the PTV, the coverage constraint must be at least 95% of the PTV_EVAL receiving 90% of the prescribed dose

9.4.2 Balloon and Strut Symmetry

The symmetry of the balloon surface or applicator struts with respect to the central lumen can have, particularly for the older single lumen balloon devices, negative effects on the dosimetric coverage of the PTV, as well as on the volume of tissue receiving more than 200% of the prescribed dose. Such asymmetry, when existent, can be corrected with the dose shaping capabilities of the multi-lumen devices. The success and degree of correction will depend on the degree of asymmetry and should be image-verified for consistency every fraction. Case-by case discretion is needed in these instances and should be discussed with the study investigators if needed.

9.4.3 Minimal Balloon/Strut Surface-Skin/Rib Distance

In this unique dose escalation trial, strict attention to skin and rib dose is critical. For the purpose of this trial, it is required that the skin and rib maximum dose is kept as low as possible, preferably at or under 100% of prescription dose. However, point maximum doses ≤ 120% of the prescription dose are allowed.

9.5 Dose Prescription and Dose Escalation

Dose fractionation scheme:

Dose level – 7.50 Gy X 3 = 22.50 Gy delivered in 3 fractions over 2-3 days

Note: A minimum of 6 hours must occur between dose fractions; a fraction interval greater than 8 hours is recommended.

9.6 Dose Delivery

Treatment utilizing the brachytherapy device should begin within 1-5 days from the acquisition of the planning CT. High dose-rate brachytherapy treatment delivery will be employed, low dose-rate dose delivery will not be allowed. The applicator will remain expanded throughout the treatment course.

Prior to each treatment, it is necessary to assure:

Continued integrity of the applicator throughout treatment, as determined by ultrasound or x-ray/CT performed prior to each delivered fraction and evaluated for any change in diameter. These should be compared to a similar study performed at the time of treatment planning. If a change in applicator geometry is noted, this should be addressed prior to additional treatment.

The patient's position in which the planning CT was obtained is reproduced prior to each fraction.

To assure proper orientation of the device throughout treatment, the orientation line will be identified and the proper alignment, as compared to the alignment at the time of planning, will be verified and corrected if any rotational deviation is seen prior to each treatment.

9.7 Quality Assurance of Dose Distribution

After target volumes have been delineated, each treatment plan shall be developed based on the dose distribution parameters listed below.

9.7.1 Acceptable

9.7.1.1 Dose volume histogram analysis of target coverage goal is ≥ 90% of the prescribed dose covering ≥ 90% of the PTV_EVAL. The volume of trapped air/fluid will be accounted for using methodology described in Section 9.4.1. A 5% adjustment will be necessary therefore confirming that ≥ 95% of the prescribed dose covering ≥ 90% of the PTV_EVAL.

9.7.1.2 Maximum skin dose will be reduced to as low as achievable while satisfying all dose parameters with a target constraint of no greater than 100% of prescription dose. A relaxation constraint not exceeding 120% of the prescribed dose is allowed.

9.7.1.3 Maximum rib dose will be reduced to as low as achievable while satisfying all dose parameters with a target constraint of no greater than 100% of prescription dose. A relaxation constraint not exceeding 120% of the prescribed dose is allowed.

9.7.1.4 The volume of breast tissue receiving 150% (V150) of the dose should be reduced to as low as achievable while satisfying all dose parameters, but should not exceed 40 cc.

9.7.1.5 The volume of breast tissue receiving 200% (V200) of the dose should be reduced to as low as achievable while satisfying all dose parameters, with a target constraint of 15 cc. The V200 should not exceed 17 cc.

9.7.1.6 For multicatheter implants, an additional metric of homogeneity, the Dose Homogeneity Index (or DHI) must be at least 0.75. The DHI is represented by the volume ratio (1-V150/V100), where V150 and V100 represent 150% of prescription dose and 100% of prescription dose respectively.

9.7.2 Unacceptable

9.7.2.1 Dose volume analysis of the target volume confirms < 90% of the prescribed dose covering < 90% of the PTV_EVAL . The volume of tapped air/fluid will be accounted for using methodology described in Section 9.4.1.

9.7.2.2 Maximum skin dose exceeds 120% of the prescribed dose.

9.7.2.3 Maximum rib dose exceeds 120% of the prescribed dose.

9.7.2.4 The volume of breast tissue receiving 150% (V150) of the dose exceeds 40 cc.

9.7.2.5 The volume of breast tissue receiving 200% (V200) of the dose exceeds 17 cc.

9.7.2.6 DHI < 0.75 (for multicatheter cases).

10. DISEASE CONTROL

The secondary endpoint of the study is local tumor control at 3 years. This will be assessed by physical examination and mammography. All cases of local failure must be proven using pathologic criteria. Note: Investigators are also asked to report any contralateral, regional (classified as an axillary, supraclavicular, internal mammary node, or skin recurrence) or distant

failure.

The location of the local ipsilateral failure in relation to the original cancer will be recorded. Criteria established by Recht et al. will be used to help classify the type of local in-breast recurrence as follows:

True Recurrence/Marginal Miss Failure (TR/MM): A TR/MM failure is defined as a recurrence of the treated cancer within or immediately adjacent to the primary tumor site.

Elsewhere Failure (E): An 'E' failure is defined as local recurrence several centimeters from the primary site and is generally believed to be a new primary cancer.

11. BREAST TOXICITIES

The primary endpoint of the study is serious toxicity rates. This will be assessed by physical examination at each follow-up visit. To be scored as a serious toxicity counting toward the primary endpoint, the toxicity must have a "probable" or "definite" attribution to the study treatment. Possible reportable toxicities to monitor include (but are not limited to) the following:

11.1 Seroma Formation

Investigators are asked to record information regarding seromas at each follow-up visit. Seromas are defined as transient, persistent, or symptomatic (e.g., causing pain or discomfort, and/or requiring therapeutic intervention) and will be monitored for (1) method of detection, (2) signs and symptoms, and (3) method of treatment.

11.2 Fibrosis

Patients will be evaluated for subcutaneous fibrosis at each follow-up visit. Fibrosis will be graded as detailed in CTCAE v4 and described in detail in the Appendix (CRF 5).

11.3 Infection

Investigators are asked to record information regarding infections at each follow-up visit. Infection will be evaluated for (1) method of detection, (2) location, (3) signs and symptoms, and (4) method of treatment.

11.4 Fat Necrosis

Investigators are asked to record information regarding fat necrosis at each follow-up visit. Fat necrosis will be evaluated for (1) method of detection, (2) signs and symptoms, and (3) method of treatment. Fat necrosis however is not a CTCAE toxicity and will not contribute to the endpoint analysis.

11.5 Pain

Investigators are asked to record information regarding pain at each follow-up visit. Pain will be evaluated for (1) location, (2) degree and extent of pain, and (3) method of treatment, and scored per CTCAE v4.

11.6 Telangiecstasia

Patients will be evaluated for telangiectasia at each follow-up visit. Telangiectasia will be graded 1-4 (Grade: 1 = less than 9 cm^2, 2 = 9-36 cm^2, 3 = greater than 36 cm^2, and 4 = whole field). Telangiectasia is not considered a serious toxicity.

11.7 Pigmentation

Patients will be evaluated for skin pigmentation at each follow-up visit. Pigmentation will be graded 1-2 (Grade: 1 = localized, <10% BSA, 2 = generalized, >10%). Pigmentation is not considered a serious toxicity.

12. COSMESIS

Cosmesis, along with toxicity, is a secondary endpoint of the study and will be assessed in several ways. In general, the assessment tools have been adapted from the current NSABP-B39 study of APBI vs. WBI, and the UK altered fractionation study discussed in Section 2.4. The 3-year evaluation of cosmesis will serve as the cosmetic endpoint.

12.1 The Breast Cancer Treatment Outcome Scale (BCTOS)

This is a self-report instrument that has high reliability and validity and will be used for evaluating patient-rated cosmesis at baseline (at time of informed consent) and at 2 years (see Appendix 7.

12.2 The Harvard Cosmesis Scale

The Harvard Cosmesis Scale is a physician-rated form based and will be used by the treating physician (surgeon or radiation oncologist) to score cosmesis at baseline (at time of informed consent) and then annually until 2 years.

Excellent: treated breast looks essentially the same as the contralateral breast as it relates to radiation effects

Good: minimal but identifiable radiation effects of the treated breast

Fair: significant radiation effects readily observable

Poor: severe sequelae of breast tissue secondary to radiation effects

12.3 Frontal Digital Photographs

Optional frontal digital photographs of both breasts will be taken at the time of consent, immediately before radiotherapy, and then annually. Two photographs will be taken, one prior to beginning treatment (preferably, prior to device placement) and one at the 2 year follow up visit. The photographs will be taken with the arms resting on the hips; they will be taken from the neck down and will not capture the face. Images will be taken by the treating physician using a dedicated camera belonging to the Radiation Oncology department. The images will be uploaded to Oncore (secure data capturing system), linked to the subject's case report forms and labeled with subject ID number and date of photo. Once images have been uploaded to Oncore, all other files can be destroyed. Comparisons of the baseline (before radiation) images and the photographs from year 2 will be scored on a 3-point scale: none/minimal change=0, mild=1, marked=2. One non-treating physician and one nurse will score each set independently.

Discrepancies will be resolved by consensus.

13. ETHICAL CONSIDERATIONS

13.1 Risks Associated with the Use of Brachytherapy Applicators

13.1.1 Surgery

Complications associated with the surgical implantation of this applicator are similar to any tumor removal surgery with the implant of a post-surgical drain. Possible complications include, but are not limited to: infection, bleeding, loss or impairment of nerve function, swelling (edema), hematoma, fluid accumulation, wound effusions, wound breakdown, ecchymosis, and scarring.

13.1.2 Applicator Implantation

Complications arising from implantation of the applicator include, but are not limited to: infection, bleeding, loss or impairment of nerve function, swelling (edema), hematoma, fluid accumulation, applicator migration, and histotoxic reactions. Device malfunction may occur after placement requiring the placement of a second replacement device or alternative treatment.

13.1.3 Brachytherapy Delivery

Complications arising from the delivery of brachytherapy (radiation treatment) include, but are not limited to: infection, loss or impairment of nerve function, swelling (edema), scarring, skin effects including dry/moist desquamation, hyperpigmentation, telangiectasia and radiation induced necrosis.

13.1.4 Imaging Procedures

As part of the clinical study patients will undergo both x-ray and ultrasound procedures and are subject to the associated risks. The risks associated with these procedures are minimal to non-existent.

13.2 Minimization of Risks

Although the risks outlined in Section 13.1 may occur, the likelihood of serious events occurring is considered uncommon. The potential risks have been minimized by:

Performing complete validation testing of the applicator; implementing appropriate quality measures into the production; and providing adequate directions for use in the labeling.

Physicians who receive the applicator practice within an institution that has completed the required physics training and are experienced in the field of oncology, surgery, and radiation therapy, which will help to minimize the risk to the patients involved.

Guidelines for patient selection and evaluation are intended to prevent the inclusion of patients who might be prone to injury due to this study, or who are inappropriate candidates for other reasons.

13.3 Potential Patient Benefits

The potential benefits of this applicator and treatment are:

Decreased likelihood of tumor recurrence

Reduction in the amount of radiation delivered to normal breast and organ tissue

Elimination of delays in systemic/local therapy

Reduction of treatment time

13.4 Informed Consent

Informed consent must be obtained prior to commencing any research procedures. This will typically be at the second visit. The PI shall seek such consent only under such circumstances that provide the prospective patient opportunity to consider whether or not to participate and that minimizes the possibility of coercion or undue influence. The information given to the patient, or the representative, shall be in a language understandable to the subject or representative. The informed consent document may not include any exculpatory language through which the subject or representative is made to waive any of the subject's legal rights or releases, or appears to release the investigator, the sponsor or the institution from liability for negligence.

Non-English Speaking Patients

Where informed consent is documented in accordance with §46.117(b)(1), the written consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. Subjects who do not speak English should be presented with a consent document written in a language understandable to them.

1. An IRB approved short form written document shall be presented in a language understandable to the subject.
2. The IRB approved English informed consent document may serve as a summary.
3. An interpreter fluent in English and the patient's language shall present the English IRB consent form offered, read it and orally present it to the patient.
4. Through the interpreter, the investigator will explain participation is voluntary and all aspects of the study, the purpose of the study, treatment plan, procedures, risks, benefits, alternatives, and the right to refuse and withdraw at any time without penalty in lay language.
5. Through the interpreter the investigator will answer any questions the patient may have.
6. The investigator shall give the subject adequate opportunity to take the IRB approved English informed consent document home for review by family and/or friends who are fluent in English and the language understandable by the patient.
7. If the patient decides to participate in the study, he/she will be asked to sign the short form document.
8. The IRB approved informed consent document will be signed by the person obtaining consent as authorized under the protocol.
9. The written short form document and the English informed consent document will be signed by the witness.

10. When the person obtaining consent is assisted by a translator, the translator may serve as a witness.
11. A copy of the signed IRB approved short form document and the English informed consent document will be given to the subject and this will be documented in the patient's medical record.
12. Through the interpreter, the investigator shall inform all patients they have the right to refuse study participation and withdraw their participation at any time without penalty and will be treated without prejudice

13.5 Institutional Review Boards

This protocol and an informed consent form will be approved initially and reviewed at least annually by an institutional review board (IRB) constituted according to regulatory and institutional requirements. The IRB granting the initial approval shall be responsible for continuing review and approval of this study including the informed consent form. A copy of the IRB's dated approval will be retained in the study files.

13.6 Economic/Financial Considerations

The treatment modalities of this protocol (brachytherapy) are standard of care and so will be paid per usual, by insurance or government agencies (charity care, Medicare, Medicaid). Patients will be responsible for their insurance required co-pays and deductibles.

14. DATA HANDLING AND RECORD KEEPING

14.1 Source Documents

Adequate original records will be maintained for the study, including (but not limited to) patient medical and surgical records, data collection forms, exam printouts, signed informed consent forms, device use records, and adverse event reports. All original source documentation will remain at the investigational site.

All investigational sites MUST PROVIDE ACTUAL COPIES OF:

The pathology report used to establish the diagnosis of breast cancer AND the radiation treatment summary report from the site.

NOTE: The patient's name and any other individually identifiable information will be removed and replaced with the patient's study identification number.

14.2 Case Report Form Completion

Case Report Forms (CRFs) can be found in the appendix of this study for each patient enrolled in the study. CRFs may be found in Appendix 8. The appropriate CRF will be completed in a legible manner in ink after each study examination. (NOTE: Any corrections will be made by drawing a single line through the incorrect entry, entering the correct information, initialing and dating the change.)

All clinical data generated in the study will be submitted to Rutgers Cancer Institute of New Jersey for quality assurance review, data entry and statistical analysis. All forms will be reviewed for completeness and evident recording errors. Questions or queries will be resolved

by contact with the clinical sites.

14.3 Reports

The investigator will submit progress reports at least once yearly and at the completion of the study to the IRB. The investigator will also submit any additional reports as requested by the IRB as a condition of study approval (e.g., safety reports, etc.).

Throughout the accrual and active treatment periods of the trial, progress reports will be prepared and presented to the Data Safety Monitoring Board (DSMB) as necessary but minimally at 6-month intervals. These reports will include an assessment of toxicities, second primary cancers and on-therapy deaths. For serious and/or unanticipated adverse events, the decision to continue the registry study will be evaluated by the DSMB as appropriate (refer to Appendix 4 for adverse event reporting criteria). After accrual is closed, adverse events and other information will be presented to the DMSB together with interim analysis results. Interim analysis will be performed annually once half of the patients have been enrolled.

14.4 Records Retention

The investigator will maintain accurate, complete and current study records during the clinical study.

15. STATISTICAL CONSIDERATIONS

15.1 Patient Accrual

Following IRB approval at all participating accrual sites, an accrual rate of 5-10 patients per month is anticipated.

15.2 Primary and Secondary Hypotheses

The primary hypothesis of this study is that the delivery of short-course APBI using a breast brachy-therapy device will result in a serious toxicity rate that is similar to that reported for conventional fractionation schemes for APBI. The secondary endpoints are that local control and cosmesis will be similar to those reported for this patient population using standard of care breast conservation therapy. Specific stopping criteria for toxicity have been defined in Section 15.3.

15.3 Sample Size Justification

The treatment will be considered unsafe if a 2-year serious toxicity rate exceeding 10% cannot be excluded with the 95% interval. Serious toxicity in this study is defined as toxicity greater than grade 2 using CTCAE v4.0 criteria. To be scored as a serious toxicity counting toward the primary endpoint, the toxicity must have a "probable" or "definite" attribution to the study treatment. In a cohort of 200 patients, there should be 11 or fewer serious toxicities to exclude a rate of 10% using the upper limit of the 95% confidence interval.

The primary purpose of this trial is to ensure that the delivery of short-course accelerated partial breast irradiation (APBI) will result in a rate of serious toxicity that is similar to that reported for conventional fractionation schemes. Specifically, the treatment will be considered safe if we are confident that the 2-year serious toxicity rate doesn't exceed 0.10. Assuming that the probability of serious toxicities with the conventional procedure is 0.03, with a sample size of 200 patients, if we observe up to 11 serious toxicities, the upper 95% confidence limit will not exceed 0.10. The relative threshold toxicity rates for different sample sizes has been generated and is available for review from the PI.

A secondary endpoint is local control. We will follow patients until the last enrolled patient has a minimum follow-up of 2 years; thus the expected median follow-up of the study population will be 3-4 years. This will allow for a Kaplan-Meier estimate of local control at 3 years. We expect local control to be greater than 95%.

In addition to toxicity, cosmesis will be followed and evaluated as a secondary endpoint. Cosmesis will be evaluated by determining the number and percent of patients within each response category (Excellent, Good, Fair, Poor) at yearly intervals. Additionally, calculating the distribution of responses after collapsing into Excellent/Good versus Fair/Poor categories will be performed. Associations between dichotomous cosmetic outcomes (Excellent/Good versus Fair/Poor) and treatment related variables will be explored.

15.4 Methods for Randomization and Stratification

This study is a non-randomized, single arm study of female patients with early stage, node-negative DCIS or invasive carcinoma receiving APBI following lumpectomy. Thus, there is no randomization or stratification. As a requirement of our study sponsors, a minimum of 50 multicatheter implant cases will be enrolled.

15.5 Outcome Measures

The primary endpoint will be measured by the data collected for toxicity and cosmesis as dichotomous variables. Time to local failure will be recorded for secondary endpoint analysis.

15.6 Statistical Analysis

All time intervals will be calculated from the date of device removal. Fisher's exact test will be performed to correlate clinical-pathological covariates with toxicity and with cosmesis. The association of variables with LR failure times will be investigated by fitting a parametric model and examining the significance of the parameter estimates. Nonparametric estimates of the survival or recurrence-free distributions or recurrence (failure) distribution will be obtained by life table methods. Tests will be declared statistically significant if the calculated *P*-value was ≤ 0.05. All tests appear as 2-sided *P*-values.

15.7 Assumptions

See Sections 15.3.

15.8 Compliance and Missing Data

Compliance will be defined as patients who complete the course of radiotherapy in a time frame as described above. If a patient is unable to do so, they will be removed from the study. Data will be accumulated on a daily basis during treatment for each patient, and then in follow-up visits. If by chance there is missing data, it will be imputed based on the population as a whole.

15.9 Interim Analysis

See Section 15.3.

16. SELECTED DEFINITIONS

Brachytherapy	Using sealed or unsealed sources for a therapeutic dose of local radiation.
Breast Conserving Surgery	Surgery where cancer is removed, together with a margin of normal breast tissue. The whole breast is not removed.
cGy	Centigray, a measure of radiation dose delivered to tissue (1 cGy = 1 rad).
Cosmesis	The appearance of the breast following treatment
Dosimetry	Measurement of radiation doses
Fraction	Radiotherapy is usually given over several weeks. The dose delivered each day is known as a fraction.
Gray or Gy	In the SI system, the unit of absorbed radiation dose
HDR	High dose-rate brachytherapy – dose rates greater than 100 cGy per hour
Margin Status (NSABP)	Positive: Tumor in contact with inked margin Negative: Tumor not microscopically in contact with the inked margin Close: Tumor within 2 mm from the inked margin
Postmenopausal	Patient must meet one of the following criteria: • A prior documented bilateral oophorectomy, or • A history of at least 12 months without spontaneous menstrual bleeding, or • Age 55 or older with a prior hysterectomy, or • Age 54 or younger with a prior hysterectomy without oophorectomy (or in whom the status is unknown), with a documented FSH level demonstrating confirmatory elevation in the lab's post-menopausal range. Patients failing to meet one of these criteria will be classified as pre-menopausal.

17. REFERENCE LIST

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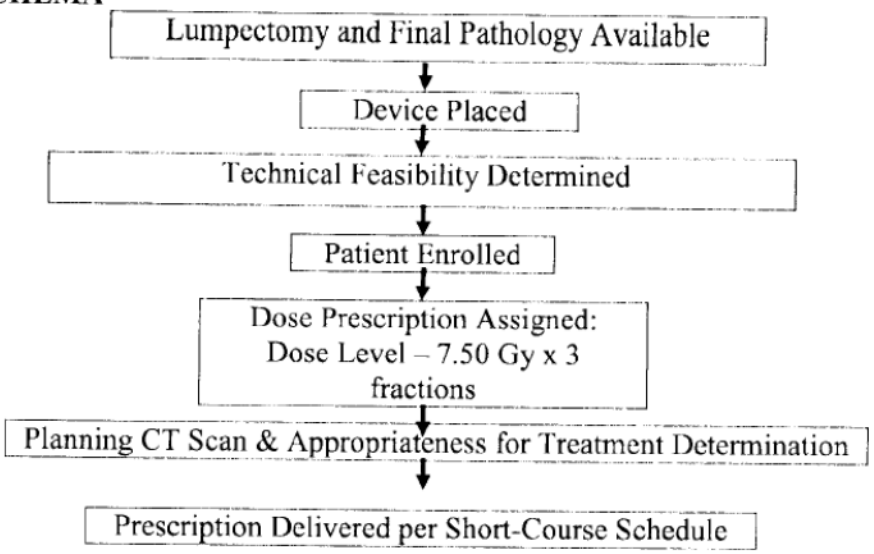
APPENDIX 1 – STUDY SCHEMA & EXAM SCHEDULE

STUDY SCHEMA

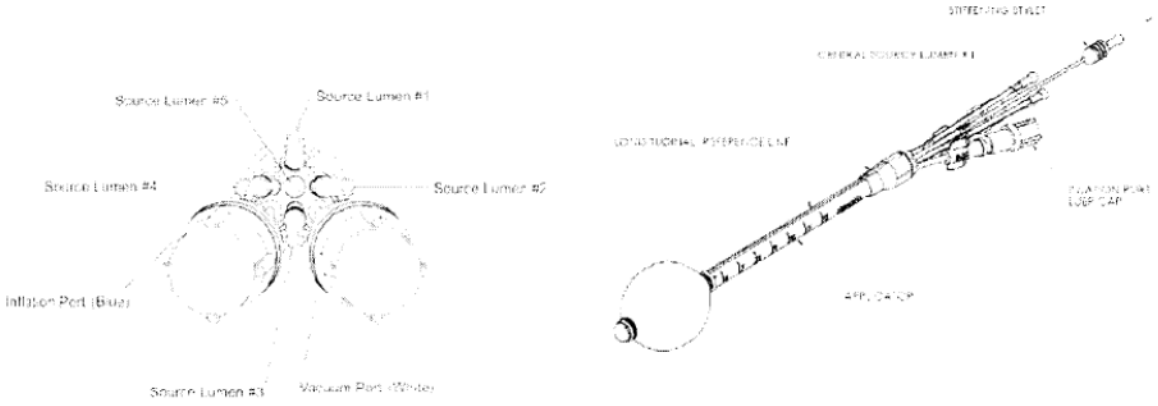


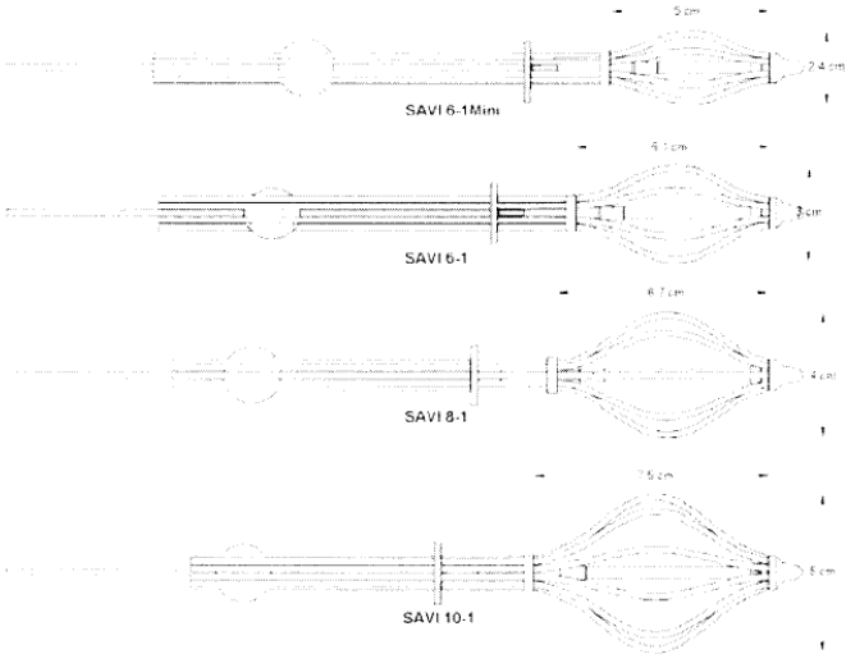
EXAM SCHEDULE

	Pre-RT Treatment	RT Treatment	Post-RT Treatment	
			2-8 Weeks	Year 1 & 2
Demographics	X			
Physical Exam, including Breast Exam	X		X	X
Pregnancy test[6]	X			
Applicator Placement	X			
Treatment Planning		X		
Brachytherapy Treatment		X		
Device Removal		X		
Disease Status Evaluation			X	X
BCTOS	X			X[5]
Harvard Cosmesis	X			X
Digital Photography	X[3]			X[3]
Toxicity Evaluations			X	X
Mammogram/MRI[1]	X[2]			X[4]

[1] MRI optional
[2] The pre-brachytherapy mammogram should be performed within 6 months of definitive surgery.
[3] Optional; at pre-treatment and 2-year follow up
[4] Mammography should be performed according to institutional standards of practice and generally performed as a baseline 6-12 months after brachytherapy and repeated annually.
[5] 2-Year Visit
[6] Women of child-bearing potential only

APPENDIX 2 – DEVICE DIAGRAM





APPENDIX 3 – INSTRUCTIONS FOR USE

DESCRIPTION

The Contura® MLB Applicator consists of a multilumen catheter attached to an inflatable spherical balloon (Figure 1). Features are provided for attachment to commercially available HDR High Dose Rate) remote afterloader equipment for passage of the radiation source delivery wire. Five radiation source wire lumens are provided: one central lumen located along the long axis of the Applicator and four curved lumens symmetrically offset from the central lumen. A removable tattooing stylet is positioned in the central lumen. Two proximal ports are also provided with Luer-type connectors for balloon inflation/deflation and for application of therapeutic vacuum.

The Contura® MLB device is provided for interstitial and diphtheritic multicatheter with spot shields, drainage catheter, three, 10 ml and one, 30 ml inflation syringes, #11 scalpel, contrast media tray, radiation source caps and labels (Figure 2).

Afterloader compatibility:
Model Flex[redacted]-15 - VariSource 2i®, VariSource iHDR and VariSource HDR a[redacted]r[redacted]
Model Flex[redacted]-15 - Classic MedPhoton afterloader (cannot be used with Classic Mod[redacted]).

Warning: The safety and effectiveness of the Contura® MLB Applicator as a replacement for whole breast irradiation in the treatment of breast cancer has not been established.

INDICATIONS FOR USE

The Contura® MLB Applicator is intended to provide brachytherapy where the physician chooses to deliver intracavitary radiation to the surgical margins following lumpectomy for breast cancer.

CONTRAINDICATIONS

- The Applicator is not intended for use in cavities that are too small, too large, or of shapes unsuitable for conformal to an approximately spherical 4 to 5 cm Diameter Sterile balloon.
- The Applicator is not intended for use in patients with internal anatomy including a highly distensible structure and/or irregular amounts of tissue surrounding the cavity that may cause the Sterile balloon to be asymmetrical.

WARNINGS

- Use caution when positioning the device tip near the chest wall of 4 cm or less to avoid unintended bodily damage.
- Do not fill the Applicator with more than 30 ml of fluid as overfilling may result in balloon rupture and/or device failure.
- The Applicator must be pre-soaked before implantation. Do not use the balloon if it is not spherical, spherical and evenly inflated.
- The breast cavity must be imaged before implantation to ensure the application will be appropriate). Do not use if the cavity is too small or if a skin surface to balloon surface distance of less than 5 mm is the result.
- To ensure appropriate irradiation dose distribution, the Applicator must be imaged prior to delivering each fraction of radiation to confirm correct position, balloon volume, skin spacing and conformance.
- If excessive resistance is encountered when attempting to remove the Applicator from the patient, surgical removal is recommended.

- Contrast media concentration of less than 10% is recommended to prevent over attenuation.
- Non-ionic contrast media is recommended for patients who are allergic to iodine based agents.

PRECAUTIONS

- The Applicator must be used only by physicians trained in catheter implantation, radiation treatment planning and delivery.
- Metal vascular clips, marking clips should not be used during the lumpectomy procedure to preserve potential radiographic features of the Contura® balloon. Care should also be taken to direct suture cuts and tails away from the cavity and whenever possible position tissue between the potential balloon surface and the tails.
- Store the Sterile Applicator at room temperature (20 to 25 C).
- Care must be taken when handling and manipulating the Contura® balloon to prevent abrasion and foreign material contamination of the balloon surface.
- A scalpel should be used to incise the skin prior to insertion of the trocar tip.
- Do not expose the device to Vacuum Port.
- Replace Luer caps and radiation lumen caps after use.
- Only clinical personnel trained in the operation of HDR afterloaders should deliver radiation using the Applicator.
- Verify that the appropriate afterloader connectors are available and function with the Applicator prior to treatment.
- Be sure that the Applicator is as sterile as possible and free of dirty beads and kinks prior to connection to the HDR afterloader.
- Inspect package before use. Do not if seal is compromised or package is damaged.

COMPLICATIONS

Complications that may be associated with the use of the Contura® MLB Applicator or the same as those associated with the use of similar devices. These may include: erythema, catheter site drainage, breast pain, tenderness, breast fibrosis, changes in breast sensation, breast seroma, breast edema, dry desquamation, dry skin, skin discoloration, pain therapy, axillary pain, fatigue, pruritis, breast retraction, nausea, skin irritation, chest hypersensitivity, hot flashes, rash, hyperpigmentation, fat necrosis, breast infection, breast fibrosis and lymphedema.

HOW SUPPLIED

The Contura® MLB Applicator and accessories are provided sterile and are intended for single patient use only.

DIRECTIONS FOR USE

- PLACEMENT - Refer to Figure 1 to 3

1. Use ultrasound to identify the lumpectomy cavity.
2. Open the Contura® MLB Applicator sterile package and remove the Applicator (A) and one 30 ml Syringe (B). Remove the Balloon Port Luer Cap (C) from

inject 30 ml of sterile saline into the Applicator and inspect for leaks and spherical symmetry. Unwind Applicator if deflected. Holding the Applicator in the introducer with the balloon hanging vertically, completely withdraw the saline from balloon.
4. Prepare a maximum 5% contrast media sterile saline solution in the 10 ml (D) provided.
5. Determine the desired point on the breast surface for the insertion of the Applicator. Insert appropriate manikin to the skin and palpate to the lumpectomy cavity. Make a skin incision with the scalpel at the insertion point of sufficient length to fully insert the Trocar (E) tip. Orient the dark marker as desired. Advance the Trocar with Split Sheath (F) into the cavity. Remove the Trocar.
6. Attach a 30 ml syringe to the Drainage Catheter (G) and drain any fluids within the cavity by inserting the Drainage Catheter through the Split Sheath and evacuate. Remove the Drainage Catheter.
7. Insert the Applicator through the Split Sheath into the cavity. Remove the Sheath.
8. Align the Radiopaque Line (I) on the catheter shaft with the 12 o'clock.
9. Remove the stiffening Stylet (J) from the Central Source Lumen (K). Attach a red radiation source lumen Cap (L).
10. Using the syringes provided, inflate the Applicator balloon with the contrast media solution to the desired fill volume. Purge any air from the fill syringes before attaching them to the Applicator.

Desired balloon diameter	Approximate balloon fill volume
4 cm	33 ml
5 cm	58 ml

11. Replace the Luer Cap on to the Inflation Port (M).
12. Use ultrasound to confirm appropriate placement, volume and cavity conformance. Final and/or verify that the Applicator balloon may be aspirated with a 30 ml Syringe attached to the white Vacuum Port (N). The volume of the balloon may be adjusted through the blue Inflation Port (M). Replace Luer Caps when finished.
13. Confirm that the radiopaque line is aligned with the skin incision.
14. Apply a surgical dressing to the exit site with the catheter positioned to minimize bending.
15. Record the final balloon fill volume on the Labels provided, and attach to the patient's chart.

- RADIATION DELIVERY - Refer to Figure 3

1. CT imaging should be used in conjunction with commercially available treatment planning software to determine the appropriate source (iridium source dwell positions and dwell times for optimal radiation delivery of a prescribed dose to the targeted treatment volume.
2. Note the orientation of the Contura® MLB Applicator with respect to the radiopaque line on the catheter shaft. Verify correct Applicator orientation, balloon position, balloon volume, skin spacing and conformance using ultrasound prior to delivery of each fraction of radiation. Adjust if necessary.
3. The Applicator's red-capped radiation source wire lumens are numbered 1 (O), 2, 3, 4 and 5 and positioned as shown in Figure 3. Lumen number 1 (O) corresponds to the offset lumen closest and parallel to the longitudinal radiopaque line (M) along the outside of the catheter. Lumen number 5 corresponds to the central lumen. Remove the red caps and use commercially available connectors to attach the source lumens to the afterloader.

Note: When using the Contura® MLB Applicator, the radioactive source length of the B011-45 Applicator must be trimmed to match using the Contura® Cut Length Guide.

4. After each treatment, replace the red caps.

• REMOVAL

1. Remove the Contura® MLB Applicator by first attaching a syringe to the blue inflation port and deflating the balloon.

Note: If difficulty is encountered deflating balloon with syringe:

1a. Re-attach syringe and vacuum to completely activate the valve. If the balloon still does not deflate, then

1b. Cut the blue Inflation Port tubing. The saline/contrast contents of the balloon will now drain from the end of the tubing.

2. Retain and withdraw inner stylet with Applicator from the cavity.

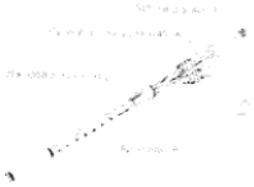


Figure 1: SENORX APPLICATOR

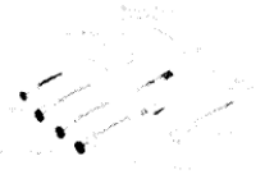


Figure 2: ACCESSORIES

Figure 3: SOURCE WIRE LUMEN ORDINATION

This product is covered by one or more of the following U.S. Patents: 6,923,754; 6,958,041; 7,211,378. Other domestic and foreign patents pending.

EXPLANATION OF SYMBOLS ON THE PACKAGE

REF	Catalog Number
	Use-By Date
LOT	Lot Number
CONT	Contents
	Sterile, Ethylene Oxide
	Attention: See Instructions for Use
2	Do Not Reuse
1	Upper Temperature Limit
	Keep away from sunlight
	Fragile

SenoRx Inc.
Aliso Viejo, California
USA

Contura

MULTI-LUMEN BALLOON SOURCE APPLICATOR FOR BRACHYTHERAPY

INSTRUCTIONS FOR USE

MODELS

B001-45
B011-45

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician

SENORX

The SAVI™ Applicator Instructions for Use

DESCRIPTION

The SAVI Applicator is an expandable cylindrical device with radially positioned catheters, which is inserted into the desired region to be treated (e.g. breast, rectum and vagina). The SAVI Applicator is provided sterile and is a single use device.

INDICATIONS

The SAVI Applicator is intended for use with commercially available remote afterloading equipment used during brachytherapy procedures. The multiple lumens of the SAVI Applicator are intended to provide pathways from which a prescribed radiation dose is delivered to the treatment area.

CONTRAINDICATIONS

As with other brachytherapy devices, treatment of tumors in generally poor condition (e.g., ulcerated) is not recommended with the SAVI Applicator.

WARNINGS

The SAVI Applicator should only be used by physicians trained in brachytherapy techniques. The physician is responsible for its proper clinical use and prescribed radiation dose. Prescribing and administering an unsuitable radiation dose may lead to clinical complications.

Prior to placement, use imaging modalities to confirm proper SAVI Applicator size. Improper sizing may result in inverted or splayed catheters.

After completion of treatment plan, verify no Applicator parts remain in the patient.

The SAVI Applicator is shipped sterile and MUST NOT BE RESTERILIZED.

The SAVI Applicator is for SINGLE USE only.

Do not use if the package is open or damaged.

The safety and effectiveness of the SAVI Applicator Kit for breast brachytherapy as a replacement for whole breast irradiation in the treatment of breast cancer has not been established.

The SAVI Applicator is compatible with the afterloader equipment listed in the table below:

Manufacturer	Afterloader	Transfer Tube
Nucletron	microSelectron Digital microSelectron V2	Transfer Tube Set 111.031 (Channels 1-9) 111.041 (Channels 10-18)
Varian Medical Systems	VariSource™ ID VariSource™ 200	Catheter Transfer Guide Tubes AL13301000 (Channels 1-10) AL13301001 (Channels 11-20)
Varian Medical Systems	GammaMed*plus*	Source Guide Tube GM11010020 (Catheter 1) GM11000370 (Catheters 2-11)

Confirm the Applicator compatibility with the afterloader (e.g. source configuration, transfer tube fittings, etc...) prior to the placement of the Applicator.

1. Select the appropriate size Applicator for treatment.

2. Attach the Expansion Tool into the fitting at the proximal end of the Applicator. No slippage in either the clockwise or counter clockwise confirms that the Expansion Tool is properly engaged.

3. Rotate the Expansion Tool in a clockwise direction until the Applicator expands to the maximum diameter.

An audible click should be noted upon maximum expansion.

4. Rotate the Expansion Tool in a counter clockwise direction until the Applicator is in a collapsed configuration.

5. Using the scalpel provided in the SAVI™ Applicator Kit, create a skin nick at the desired point of entry.

6. Through the skin nick and using ultrasound guidance, advance the obturator and sheath provided in the SAVI Applicator Kit into the cavity. Always align the long axis of the obturator to the long axis of the cavity.

7. Retract the obturator, leaving the sheath in place.

8. Insert the Applicator through the sheath until the distal tip of the device contacts the far wall of the cavity.

9. Rotate the Expansion Tool in a clockwise direction until the Applicator expands to the desired diameter.

10. Once the placement of the Applicator is confirmed via image guidance, carefully retract the Catheter Protector from the center catheter.

11. Remove the Expansion Tool and carefully reinsert the catheter protector.

Optional: The SAVI Prep™ catheter may be inserted into the desired region to be treated at the time of lumpectomy or just prior to placement of the SAVI applicator. This balloon-type catheter acts as a volume indicator for the anatomical site and subsequent cavity evaluation prior to placement of the SAVI applicator.

1. Under ultrasound guidance advance the SAVI Prep catheter through the sheath until the distal tip of the device contacts the far wall of the cavity.

2. Inflate the SAVI Prep catheter with sterile solution to the desired fill volume. Refer to the chart for fluid fill volumes and the corresponding SAVI applicator model*:

Fill Volume	SAVI Applicator Model
20 cc	6-1Mini
30 cc	6-1
40 cc	8-1
60 cc	10-1

*This chart is for reference only. It is not intended to replace clinician discretion.

3. Prior to placement of the SAVI applicator, attach syringe to the luer fitting at the distal end of the SAVI Prep catheter and withdrawn all the fluid from the balloon.

4. Gently remove the SAVI Prep catheter and discard.

RADIATION THERAPY DELIVERY

Prior to delivering brachytherapy fractions, verify the SAVI Applicator position. Follow internal QA procedures to assure appropriateness of the treatment plan.

During periods when the SAVI Applicator is not being used for brachytherapy treatment, carefully insert the appropriate size Catheter Protector into each of the applicator catheters.

a. The short protectors, with a working length of 7.75", are used in the outer catheters of the applicator
b. The longer protector, with a working length of 10", is used in the central catheter of the applicator

1. Prior to administering a brachytherapy treatment fraction, carefully retract the Catheter Protector from each of the catheters.

2. With the central catheter straightened, re-insert the Expansion Tool into the fitting at the proximal end of the Applicator. No slippage in either the clockwise or counter clockwise confirms that the Expansion Tool is properly engaged.

3. Attach the Applicator catheters to the afterloader transfer tubes using the desired numerical sequence.

4. Confirm that the afterloader transfer tubes have a straight pathway between the afterloader and the Applicator. If necessary, support proximal end of the SAVI Applicator to maintain proper positioning.

5. After completion of the brachytherapy treatment fraction, disconnect the transfer tubes and carefully reinsert the Catheter Protectors into each of the catheters.

REMOVAL OF APPLICATOR

After the prescribed radiation treatment plan has been completed:

1. Disconnect the transfer tubes from the Applicator.

2. Attach the Expansion Tool into the fitting at the proximal end of the Applicator.

3. Rotate the Expansion Tool in a counter clockwise direction until the Applicator is in a collapsed configuration.

4. Gently remove the Applicator and discard.

DISPOSAL PROCEDURES

It is the user's responsibility to dispose of all parts according to local regulations. Upon disposal of the product or related parts, it is suggested to:

- Check the part for radioactive contamination
- Disinfect the parts prior to disposal
- Dispose of sharp objects in a safe manner

STORAGE

Store at room temperature. Avoid storing the SAVI Applicator at conditions of excessive heat or humidity.

APPENDIX 4 – ADVERSE EVENT REPORTING

The investigator should report all serious adverse events that occur during the study.

Serious Adverse Event (SAE)

A serious adverse event is defined as follows:

1) Death or threat to life;

2) Permanent impairment of a body function or permanent damage to a body structure; or

3) Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

4) Requires unexpected inpatient hospitalization or prolongation of existing hospitalization

All serious adverse events are to be reported to the Rutgers Cancer Institute's Office of Human Research within 5 days of learning of the adverse event.

Examples of serious events include: necrosis, non-wound healing, moist desquamation (that does not resolve within 4 weeks), unresolved bleeding, infection requiring medical or surgical intervention, pneumothorax, acute pneumonitis, seroma/hematoma (symptomatic and/or cosmetically deforming), rib fracture, severe pain (not resolving within the first month and requiring narcotics) and wound dehiscence.

Events not considered serious include: erythema, infection (or suspected infections, i.e., fever) treated only with antibiotics, and seroma/hematoma (asymptomatic and/or not deforming).

APPENDIX 5 – BREAST CANCER TREATMENT OUTCOME SCALE (BCTOS)

BCTOS SELF-ASSESSMENT

Patient ID Number: ___ ___ – ___ ___ ___ ___ (Site) Visit Date: ___ ___ / ___ ___ / ___ ___ (M M / D D / Y Y) or ☐ not done

INSTRUCTIONS:

You are participating in a research study that compares cosmetic and functional outcomes after breast cancer therapy. The self-reported questionnaire below will assist your doctors in comparing the outcomes from this study to those for other breast cancer patients.

We are interested in your evaluation of your physical appearance and functioning since breast surgery. Please rate the following items on this four-point scale:

☐ 1	No difference between treated and untreated breast and area
☐ 2	Slight difference between treated and untreated breast and area
☐ 3	Moderate difference between treated and untreated breast and area
☐ 4	Large difference between treated and untreated breast and area

ITEMS:

A	Breast size	☐ 1	☐ 2	☐ 3	☐ 4
B	Breast texture	☐ 1	☐ 2	☐ 3	☐ 4
C	Nipple appearance	☐ 1	☐ 2	☐ 3	☐ 4
D	Shoulder movement	☐ 1	☐ 2	☐ 3	☐ 4
E	Arm movement	☐ 1	☐ 2	☐ 3	☐ 4
F	Breast pain	☐ 1	☐ 2	☐ 3	☐ 4
G	Ability to lift objects	☐ 1	☐ 2	☐ 3	☐ 4
H	Breast tenderness	☐ 1	☐ 2	☐ 3	☐ 4
I	Shoulder stiffness	☐ 1	☐ 2	☐ 3	☐ 4
J	Breast elevation (how high the breast is)	☐ 1	☐ 2	☐ 3	☐ 4
K	Scar tissue	☐ 1	☐ 2	☐ 3	☐ 4
L	Shoulder pain	☐ 1	☐ 2	☐ 3	☐ 4
M	Arm pain	☐ 1	☐ 2	☐ 3	☐ 4
N	Arm stiffness	☐ 1	☐ 2	☐ 3	☐ 4
O	Fit of bra	☐ 1	☐ 2	☐ 3	☐ 4
P	Breast sensitivity	☐ 1	☐ 2	☐ 3	☐ 4
Q	Fit of clothing	☐ 1	☐ 2	☐ 3	☐ 4

APPENDIX 6 – DRAFT CASE REPORT FORMS
CRF #1 – PRE-RT TREATMENT

Patient ID Number: ___ ___ – ___ ___ ___ ___ (Site) Date ICF Signed: ____/____/____ (M M D D Y Y)

DEMOGRAPHICS

1. Date of Birth: ____/____/____ (M M D D Y Y)	2. Age at Entry: _____ years
3. Menopausal Status: ☐ Pre/Peri ☐ Post (***Note: refer to protocol for definition)***	
4. Race: ☐ Asian ☐ Black ☐ Caucasian, non-Hispanic ☐ Caucasian, Hispanic ☐ Other_____	

BREAST EXAM/CANCER FINDINGS

5. Breast Cup Size: ☐ A ☐ B ☐ C ☐ D ☐ Not Measured	6. Breast: ☐ Right ☐ Left
7. Lesion Location: ☐ UIQ ☐ LIQ ☐ Central ☐ UOQ ☐ LOQ	
8. Lumpectomy Date: ____/____/____ (M M D D Y Y)	9a. Closed Cavity Placement: ☐ Yes ☐ No 9b. Was CED Used: ☐ Yes ☐ No
10. Histology: ☐ Pure DCIS ☐ Invasive Ductal ☐ Invasive Lobular ☐ Other _____	
11. Tumor Size at largest diameter: _____ mm	12. Tumor Grade: ☐ I ☐ II ☐ III
13. AJC Classification: ☐ Tis ☐ T1 ☐ T2, ≤ 3 cm ☐ T2, > 3 cm ☐ ≥ T3 ***Note: T2 > 3cm & ≥ T3 do not qualify for study***	
14. AJC Stage: ☐ 0 ☐ I ☐ II	
15. Surgical Margin: ☐ Negative (no tumor on ink) ☐ Close (tumor within 2 mm of ink) ☐ Positive (tumor in contact with ink) ***Note: Positive margin does not qualify for study***	

Questions 16a-16e: **If DCIS, or ☐ n/a**	16a. Grade: ☐ NGI ☐ NGII ☐ NGIII	16b. Architectural Pattern: *(check all that apply, rate by priority with 1=Greatest and 5=Lowest)* ☐ Comedo _____ ☐ Cribiform _____ ☐ Papillary _____ ☐ Micro Papillary _____ ☐ Solid _____	16c. Necrosis: ☐ Absent ☐ Central ☐ Comedo ☐ Focal ☐ Punctate ☐ Other _____
	16d. Sentinel Node Biopsy: ☐ Yes ☐ No	16e. SNB Result: ☐ Negative ☐ Positive ☐ n/a ***Note: Positive result does not qualify for study***	

Questions 17a-17b: **If invasive, or ☐ n/a**	17a. Axillary Staging Procedure: ☐ Sentinel Node Biopsy ☐ Axillary Dissection, # Excised ____	17b. Axillary Staging Result(s): ☐ Negative ☐ Positive ***Note: Positive result does not qualify for study***

18. Estrogen Receptor:	☐ Positive	☐ Negative		
19. Progesterone Receptor :	☐ Positive	☐ Negative	☐ Unknown	☐ Not done
20. Her2Neu:	☐ Positive	☐ Negative	☐ Unknown	☐ Not done

21. FISH:	☐ Amplified	☐ Non-Amplified	☐ Not done
22. Did Patient Qualify for Study Treatment:	☐ Yes	☐ No	***If No, Complete CRF #6 "Exit"***

Treating Physician Signature: _____ Date: _____

CRF #2 – RT TREATMENT

Patient ID Number: ___ ___ – ___ ___ ___ ___
Site

Radiation Oncologist: _____

Surgeon: _____

DEVICE PLACEMENT

1. Date: ____/____/____ M M D D Y Y	2. Location of Device Placement: ☐ OR ☐ Office ☐ Other_____

Contura ☐ 4-5 cm ☐ 5-6 cm

SAVI ☐ 2.4 cm/6-1 mini ☐ 3 cm/6-1 ☐ 4 cm/8-1 ☐ 5 cm/10-1

4. Balloon Volume: _____ cc

5. Balloon Diameter: _____ mm

6. Minimum Skin Spacing: _____ mm	7. Minimum Rib Spacing: _____ mm

8. Balloon Conformance – Air/Seroma Volume, or ☐ n/a: Before Vacuum _____ cc After Vacuum _____ cc
Note: the volume of trapped air/fluid must be < 10%of the PTV_EVAL

9. Balloon Symmetry: Central Lumen Asymmetry/Deviation _____ mm ***Note: R2-R1/2 where the larger radius=R2***

TREATMENT PLANNING

10. Maximum Skin Dose: _____ % of PD	11. Maximum Rib Dose: _____ % of PD
12. PTV_EVAL Volume: _____ cc	13. Volume of tissue receiving 100, 150, 200 PD 16a. V100 _____ cc 16b. V150 _____ cc 16c. V200 _____ cc
14. % of Prescribed Dose: 15a. _____ % of PD to 100% of PTV_EVAL 15b. _____ % of PD to 95% of PTV_EVAL 15c. _____ % of PD to 90% of PTV_EVAL	

TREATMENT

15. RT Start Date: ____/____/____ M M D D Y Y	16. Source Strength at Fraction 1: _____ Ci	17. Step Size: ☐ 5 mm ☐ Other _____

18. By Fraction – Total Number of Dwell Positions: ***(check all that apply)***

													Total Dwell Time Fraction 1
Lumen 1:	☐ n/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	☐ Other _____	_____ sec
Lumen 2:	☐ n/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	☐ Other _____	_____ sec
Lumen 3:	☐ n/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	☐ Other _____	_____ sec
Lumen 4:	☐ n/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	☐ Other _____	_____ sec
Lumen 5:	☐ n/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	☐ Other _____	_____ sec
Lumen 6:	☐ n/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	☐ Other _____	_____ sec
Lumen 7:	☐ n/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	☐ Other _____	_____ sec
Lumen 8:	☐ n/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	☐ Other _____	_____ sec
Lumen 9:	☐ n/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	☐ Other _____	_____ sec
Lumen 10:	☐ n/a	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	☐ Other _____	_____ sec

19. Dose per Fraction: ☐ 7.5 Gy ☐ Other	20. Number of Fractions: ☐ 3 ☐ Other
21. RT Stop Date: ____/____/____ M M D D Y Y	22. Removal Date: ____/____/____ M M D D Y Y

Treating Physician Signature: _____ Date: _____

CRF #3 – POST-RT FOLLOW-UP VISITS

Patient ID Number: ___ ___ – ___ ___ ___ ___ (Site) Visit Date: ___/___/___ (M M D D Y Y)

DISEASE CONTROL (NEW FAILURE SINCE LAST VISIT): ☐ **N/A (GO TO QUESTION 10) OR COMPLETE BELOW**

Local Ipsilateral Failure

1. Failure Date: ___/___/___ (M M D D Y Y)

2. If True Recurrence/Marginal Miss (TR/MM), or ☐ n/a:
   Biopsy Results: ☐ Invasive ☐ Non-Invasive
   Grade ☐ I ☐ II ☐ III
   Receptor Status _____

3. If Elsewhere (E), or ☐ n/a:
   Biopsy Results: ☐ Invasive ☐ Non-Invasive
   Grade ☐ I ☐ II ☐ III
   Receptor Status _____

Contralateral Failure

4. Failure Date: ___/___/___ (M M D D Y Y)

5. Biopsy Results: ☐ Invasive ☐ Non-Invasive
   Grade ☐ I ☐ II ☐ III Receptor Status _____

Regional Failure

6. Failure Date: ___/___/___ (M M D D Y Y)

7. Location: ☐ Axilla ☐ Internal Mammary Nodes ☐ Skin
   ☐ Supraclavicular Fossa ☐ Other _____

Distant Failure

8. Failure Date: ___/___/___ (M M D D Y Y)

9. Location: ☐ Lung ☐ Bone ☐ Other _____

COSMESIS

10. Cosmetic Evaluation of Breast (Harvard Scale, or ☐ not done: *(Note: required at annual visits)*

☐ Excellent	The treated breast looks essentially the same as the opposite breast
☐ Good	Minimal but identifiable effects of radiation on the treated breast
☐ Fair	Significant effects of radiation on the treated breast
☐ Poor	Severe normal tissue sequelae secondary to radiation

BREAST TOXICITIES

11. Complication Assessment, ☐ n/a or ☐ not done: *(Note: required at all visits, check all that apply)*

***Submit a NEW CRF #4/5 for each new toxicity; Complete a separate CRF for each toxicity**
**** R/W=Resolution or Worsening – Follow Instructions on CRF #4 to resolve/amend this toxicity**
***** U/I=Unchanged or Improvement without Resolution -- No change to CRF #4**

11a. Seroma Formation	☐ Not Evident	Since Last Visit:	☐ New*	☐ R/W**	☐ U/I***
11b. Infection	☐ Not Evident	Since Last Visit:	☐ New*	☐ R/W**	☐ U/I***
11c. Dermatitis	☐ Not Evident	Since Last Visit:	☐ New*	☐ R/W**	☐ U/I***
11d. Pain	☐ Not Evident	Since Last Visit:	☐ New*	☐ R/W**	☐ U/I***
11e. Ulceration	☐ Not Evident	Since Last Visit:	☐ New*	☐ R/W**	☐ U/I***
11f. Fibrosis	☐ Not Evident	Since Last Visit:	☐ New*	☐ R/W**	☐ U/I***
11g. Other	☐ Not Evident	Since Last Visit:	☐ New*	☐ R/W**	☐ U/I***

ADJUVANT THERAPY

12. Adjuvant Therapy for this Cancer Episode, or ☐ n/a: *(Check all that apply)*
   ☐ Hormonal Therapy – Type _____
   ☐ Chemotherapy – Type _____ Chemotherapy Start Date: ___/___/___ (M M D D Y Y)
   ☐ Other _____

Treating Physician Signature: _____ Date: _____

CRF #4 – TOXICITIES/ADVERSE EVENT FORM

Patient ID Number: ___ ___ – ___ ___ ___ ___ (Site) Visit Date: ____/____/____ (M M D D Y Y)

New Toxicity – Complete a NEW CRF; Report only ONE toxicity per CRF.

Resolution of Ongoing Toxicity – Amend the original CRF for this toxicity (do not rewrite it). Cross through the "ongoing" response (#4) and provide the resolution date (#5).

Worsening of Ongoing Toxicity – A toxicity that worsens must first be "resolved" at the previous severity. Amend the original CRF for this toxicity (do not rewrite it). Cross through the "ongoing" response (#4) and provide the "resolution" date (#5). Then start a NEW CRF for the new severity. The resolution date for the first report and the start date for the new CRF should be the same.

1. Toxicity:

☐ Fibrosis	☐ Dermatitis	☐ Seroma	☐ Pain
☐ Telangiectasia	☐ Fat necrosis	☐ Infection	☐ Ulceration
☐ Rib fracture	☐ Pneumonitis	☐ Cardiac toxicity	☐ Bleeding
☐ Non-healing wound	☐ Wound dehiscence	☐ Other _____	

2. Report Type: ☐ New ☐ Resolved

3. Onset Date: ____/____/____ (M M D D Y Y)

4. Ongoing ☐

5. Resolution Date: ____/____/____ (M M D D Y Y)

6. Method of Detection, or ☐ n/a: *(check all that apply)*
- ☐ Clinical
- ☐ CT Scan
- ☐ Patient
- ☐ Physician
- ☐ Radiographic
- ☐ Ultrasound
- ☐ Other _____

7. Symptomatic, or ☐ n/a: *(check all that apply)*
- ☐ Fever
- ☐ Mass
- ☐ Pain
- ☐ Sepsis
- ☐ Swelling
- ☐ Other _____

8. Method of Treatment, or ☐ n/a: *(check all that apply)*
- ☐ Analgesic, Narcotic
- ☐ Analgesics, Non-Narcotic
- ☐ Antibiotics, IV
- ☐ Antibiotics, Oral
- ☐ Aspiration
- ☐ Non-Steroidal NSAID
- ☐ Observation
- ☐ Surgical Excision
- ☐ Other_____

9. Location, or ☐ n/a: *(check all that apply)* ☐ Arm ☐ Axilla ☐ Breast ☐ Chest Wall ☐ Other _____

10. IS THIS AN SAE: ☐ YES ☐ NO

11. Relationship to Study Treatment: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite

12. Grade or ☐ n/a: ☐ Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4

*** Also Complete CRF # 5"TOXICITIES-CTCAEV4 GRADED TOXICITIES if applicable"**

Treating Physician Signature: _____ Date: _____

CRF #5 – TOXICITIES- CTCAEV4 GRADED TOXICITIES

Patient ID Number: ___ ___ -- ___ ___ ___ ___ (Site) Visit Date: ___/___/___ (M M D D Y Y)

Grade	1	2	3	4
Breast infection		Local infection with moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	Severe infection; axillary adenitis; IV antibacterial, antifungal, or antiviral intervention indicated	Life-threatening consequences; urgent intervention indicated
Fibrosis, deep connective tissue	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g. mouth, anus); limiting self care ADL)	Generalized; associated with signs or symptoms of impaired breathing or feeding
Superficial soft tissue fibrosis	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g. mouth, anus); limiting self care ADL)	Generalized; associated with signs or symptoms of impaired breathing or feeding
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	
Dermatitis, radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated
Seroma	Asymptomatic; clinical or	Symptomatic; simple	Symptomatic, elective radiologic or operative	

	diagnostic observations only; intervention not indicated	aspiration	intervention indicated	
Skin induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration, unable to slide or pinch skin; limiting joint movement or orifice (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding
Skin Ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	
Radiation recall reaction (dermatologic)	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated

*** Also Complete CRF #4 "TOXICITIES/ADVERSE EVENTS"**

Treating Physician Signature: _____ Date: _____

CRF #6 – EXIT

Patient ID Number: ___ ___ – ___ ___ ___ ___ (Site) Exit Date: ___/___/___ (M M D D Y Y)

STUDY EXIT

1. Outcome:	☐ Completed (proceed to section 4) ☐ Discontinued (specify reason in section 2)
2. Discontinuation Reason: *(check one)*	☐ Patient did not Qualify for Enrollment ☐ Patient did not Receive Device ☐ Patient's Voluntary Withdrawal ☐ Patient's Inability to Continue (i.e., moved, personal reasons, etc) ☐ Patient is Lost to Follow-up (reasons unknown) ☐ Investigator's Discretion (specify reason in section 3) ☐ Death (*Note: Exit Date should be Date of Death)* ☐ Other _____
3. Comments, or ☐ none:	_____ _____ _____
4. Investigator Review:	I certify that I have reviewed all case report forms for accuracy and completeness. Investigator's Signature: _____ Date: ___/___/___ (M M D D Y Y)

[redacted]

CONSENT TO TAKE PART IN A RESEARCH STUDY

TITLE OF STUDY : TRI-fraction Radiotherapy Utilized to Minimize Patient Hospital Trips (TRIUMPH-T): A Phase II trial

PRINCIPAL INVESTIGATOR: [redacted]

STUDY-RELATED PHONE NUMBER(S): [redacted]

This consent form is part of an informed consent process for a research study and it will provide information that will help you to decide whether you wish to volunteer for this research study. It will help you to understand what the study is about and what will happen in the course of the study.

If you have questions at any time during the research study, you should feel free to ask them and should expect to be given answers that you completely understand.

After all of your questions have been answered, if you still wish to take part in the study, you will be asked to sign this informed consent form.

The study doctor, Bruce Haffty, MD, or another member of the study team will also be asked to sign this informed consent. You will be given a copy of the signed consent form to keep.

You are not giving up any of your legal rights by volunteering for this research study or by signing this consent form.

Even after signing this consent form, you may withdraw from the study at any time.

Sponsor of the study: This research is paid for in part by the makers of the devices (Elekta and Cianna) and in part by the Rutgers Cancer Institute of New Jersey.

Why is this study being done?

You may be able to have breast conserving surgery which would only remove the cancer from the breast. The surgery is called lumpectomy or lump removal. Radiation therapy is usually given after this surgery to improve control of the cancer within the breast.

Radiation therapy uses a type of energy to kill cancer cells and shrink tumors. It destroys cells in the area being treated by damaging their genetic matter. This makes it impossible for these cells to keep growing and dividing. Radiation damages both cancer cells and normal cells, but most normal cells can recover and function properly. The goal of this treatment is to damage as many

cancer cells as possible, while limiting harm to nearby healthy tissue. This therapy includes 5 to 6 weeks of external treatment to your whole breast.

Brachytherapy is a type of internal radiation therapy. It provides radiation inside your breast to any remaining tumor cells next to the space where the tumor was removed. It does not treat your whole breast and is given over a shorter amount of time (5-8 days). This study utilizes FDA cleared devices to provide brachytherapy. Two of the devices used in this study are called the Contura MLB applicator and the SAVI applicator. Also, your doctor may use several thinner tubes, or catheters, to treat the area at risk. Your treating physician will decide which applicator or method is more appropriate for use based on the size, shape and location of the surgical space created by the lumpectomy. The devices allow your doctor to send your radiation therapy into this space created by your lumpectomy.

The standard treatment time for this type of partial breast therapy is 5 to 8 days. This study is investigating a change in the dose delivery to reduce the overall time to 2-3 days. After the radiation therapy regimen, the device will be removed.

Why have you been asked to take part in this study?
You are being asked to take part in this study because you have had breast conserving surgery (lumpectomy) for breast cancer.

Who may take part in this study? And who may not?
You may take part in this study if you are at least 45 years of age with breast cancer. You will have tests and exams to see if you can take part in this study. Additionally you may take part if:

- You have had a lumpectomy to remove the cancer
- You are able to make your treatment and follow up appointments
- You have read and signed this consent form

You may not take part in this study if:
- You have previously received radiation to the breast or chest area
- You have had breast cancer in the past
- You are pregnant or breast feeding

How long will the study take and how many subjects will participate?
You will be in the study for up to 6 years. You will receive radiation therapy on study for 2-3 days and then will continue follow up visits for 2 years. After 2 years you will have to completed study visits; however the study doctor will continue to review your medical record to check the status of your disease.

A total of 200 patients will take part in this study. You will be one of approximately 30 patients enrolled at the Rutgers Cancer Institute of New Jersey.

What will you be asked to do if you take part in this research study?
Before you begin study treatment:
You will have some exams, tests and procedures to find out if you can take part in this study.

Most of these exams, tests and procedures are part of regular cancer care and may be done even if you do not join the study. If some of these have been done recently they may not need to be repeated, this will be up to the study doctor.

- Physical exam, including breast exam
- Mammogram
- MRI (Magnetic Resonance Imaging), this will be up to the study doctor

The study device or catheters will be put in the cavity left behind after your tumor was taken out. The end of the tubes will be on the outside of your breast. The balloon is filled with an X-ray dye and saline (salt solution) to inflate the treatment device to the correct size and shape. The treatment device will be expanded to the correct size and shape. CT scans, X-rays and ultrasound imaging may be done to confirm the size, shape and location of the balloon. These images will be used to confirm that you should receive radiation therapy with the device. Your doctor will describe the exact details of your individual treatment regimen.

It is possible that based on the location or shape of the device in the breast, you are no longer eligible for the experimental treatment. In this case your doctors will either treat you with the usual 5 day course of treatment, or they may elect to remove the device altogether and discuss other options of therapy, such as standard external beam radiation over 4-6 weeks, with you.

While on study treatment:
If the exams, tests and procedures show that you can be in the study and you choose to take part you will be enrolled and scheduled to start radiation therapy on study.

In general, the radiation therapy portion of your treatment will begin within 5 days after the device has been placed in your breast. The treatment will be delivered with 3 doses of radiation delivered over two or three days. If you are treated over 2 days, you will be asked to come in twice a day for one day of your treatment, with at least a 6 hour break between the two treatments. Each individual treatment time will last between 15 minutes to an hour depending on your exact prescription. Before each radiation therapy dose, a CT scan, x-ray or ultrasound will be done to make sure the device is correctly in place. During each treatment, the radiation is inserted into the tube of the device. At the end of each individual treatment, the radiation is removed from the tube of the device. At the end of your entire course of radiation therapy, the device will be deflated and removed.

After you have completed study treatment:
After your radiation therapy is completed, you will still be seen by your doctor. The visits will be planned according to your doctor's routine follow-up visit schedule. These visits are important to monitor your ongoing control of the cancer within your breast.

- 2-8 weeks after completing treatment, you will return to see the doctor for a physical exam, including breast exam and evaluation of any side effects
- Then at year 1 and 2:
    - Physical exam, including breast exam
    - Evaluation of any side effects
    - Mammogram (6-12 months after completing treatment, then annually).

Study Specific Exams:

The following exams, tests and procedures are not part of regular cancer care. These are being done because you are on study.

Questionnaires:

You will be asked to complete a questionnaire. These are being done to help doctors determine how the treatment is affecting your physical appearance and functioning since breast surgery. The questionnaire should take about 5 minutes to complete, if any of the questions make you feel uncomfortable, you do not have to answer them. You will be asked to complete the questionnaire:

- Before starting radiation therapy;
- At your 2 year follow up visit

Frontal Digital Photographs:

The study doctors want to know how the radiation treatment affects the breast visually. This will be done by taking photographs of both breasts. The photographs will be taken from the neck down and will not include your face. This is optional. If you agree now, you may change your mind at any time. If you agree to allow photographs to be taken, then a photograph will be taken, with the arms resting on the hips at the following time points:

- Prior to beginning treatment;
- At your 2 year follow up visit.

Do you agree to have frontal digital photographs taken?

YES _____ NO _____

What are the risks and/or discomforts you might experience if you take part in this study?

RISKS

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or serious. You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to implanting the device may include, but are not limited to:

- Infection
- Bleeding
- Loss of or injury to nerve function
- Swelling
- Blood clotting
- Fluid buildup
- Device movement
- Allergic reactions
- Scar or mark (there may be a small mark where the device entered the skin)

Risks and side effects related to the radiation treatment may include, but are not limited to:

- Infection
- Loss of or injury to nerve function
- Swelling
- Rib fracture
- Lung inflammation
- Chest wall pain
- Skin redness
- Skin peeling and/or ulceration
- Tissue death

Long-term side effects from radiation treatment may include, but are not limited to:

- Scarring
- Firmness
- Tenderness
- Pain
- Cosmetic change
- Deformity in the treated area of the breast

Women who are pregnant or nursing may not take part in this study. Before entering the study, you and your study doctor may need to agree on the method of birth control you will use during the study. If you think you have gotten pregnant during the study, you must tell your study doctor immediately.

Are there any benefits for you if you choose to take part in this research study?

It is not possible to state that you will benefit from this treatment. One possible benefit of this treatment is reduced treatment time. While doctors hope this type of shorter treatment will be more useful against cancer compared to the usual treatment, there is no long-term proof of this yet. We do know that the information from this study will help doctors learn more about brachytherapy as a treatment for cancer. The potential benefit to society is the development of a new way to deliver radiation to the tumor cells in the area where the tumor was and kill any remaining tumor cells. This new method is designed to spare normal tissue from radiation effects and deliver the treatment more time efficiently.

What are your alternatives if you don't want to take part in this study?

If you decide not to enter this study, there are non-research treatments available to you. Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

How will you know if new information is learned that may affect whether you are willing to stay in this research study?

You will be told about any new information that might change your decision to be in this study. You may be asked to sign a revised consent form if this occurs.

Will there be any cost to you to take part in this study?

You and/or your health plan/insurance company may need to pay for some or all of the costs for treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. In general, a shorter treatment such as this is much less expensive for your health plan/insurance than the standard 5 day treatment. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company any more than the cost of getting regular cancer treatment.

If you have any questions about insurance coverage, including any out of pocket expenses you might incur, or which laboratory or facilities you are allowed to have tests at, a financial counselor will be made available to you upon request.

Will you be paid to take part in this study?
You will not receive any payment for your participation in this study.

How will information about you be kept private or confidential?

All efforts will be made to keep your personal information in your research record confidential, but total confidentiality cannot be guaranteed. Your personal information may be given out if required by law.

Information about your cancer and treatment will be collected from your medical record for the study. The information will be with a study identification number and stored in a secured electronic file. The electronic file is password protected and accessible only to authorized study personnel.

If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What will happen if you are injured during this study?
Subjects in this study will be exposed to certain risks of personal injury in addition to those associated with standard forms of treatment, which were discussed in the Risk and Discomforts section of this consent form. In addition, it is possible that during the course of this study, new adverse effects of the catheters, SAVI applicator, or Contura MLB applicator that result in personal injury may be discovered. The University will make appropriate referrals for medical and/or dental treatment for subjects who sustain personal injuries or illnesses as a direct consequence of participation in the research. The subject's health insurance carrier or other third-party payer will be billed for the cost of this treatment; provided that the University shall not submit to federally funded programs, e.g., Medicare, Medicaid or CHAMPUS, for reimbursement first if submission to such programs is prohibited by law. No financial compensation will be provided by the University and no other type of assistance is available from the University.

You are not giving up any of your legal rights by signing this informed consent form or by taking

part in this research study.

What will happen if you do not wish to take part in the study or if you later decide not to stay in the study?
Participation in this study is voluntary. You may choose not to participate or you may change your mind at any time.

If you do not want to enter the study or decide to stop participating, your relationship with the study staff will not change, and you may do so without penalty and without loss of benefits to which you are otherwise entitled.

You may also withdraw your consent for the use of data already collected about you, but you must do this in writing to:

[redacted]

At any time, the study doctor can take you out of this study because it would not be in your best interest to stay in it, even if you are willing to stay in the study.

If you decide to withdraw from the study for any reason, you may be asked to return for at least one additional visit for safety reasons.

Who can you call if you have any questions?

If you have any questions about taking part in this study or if you feel you may have suffered a research related injury, you can call the study doctor:

[redacted]

If you have any questions about your rights as a research subject, you can call:

IRB Director
[redacted]

What are your rights if you decide to take part in this research study?

You have the right to ask questions about any part of the study at any time. You should not sign this form unless you have had a chance to ask questions and have been given answers to all of

your questions.

PERMISSION (Authorization) TO USE OR SHARE HEALTH INFORMATION THAT IDENTIFIES YOU FOR A RESEARCH STUDY

Information about you and your health is personal and private, so this information generally cannot be used in research without your written permission. The next few paragraphs tell you about how researchers want to use and share your health information in this research study. Your information will only be used as described here or as allowed or required by law. Ask questions if you do not understand any part of the research or the use of your health information. If you sign this consent form, you agree to let the researchers use your information in the research and share it with others as described below.

What is the purpose of the research and how will my information be used?

You are being invited to take part in this research study which is described at the beginning of this form. The purpose of collecting and using your health information for this study is to help researchers answer the questions that are being asked in the research.

What information about me will be used?

If you choose to be in this study, the study doctor will get your personal and medical information. This information may include:

- Past and present medical records
- Research records
- Records about your study visits
- Physical exams
- Laboratory, x-rays, CT scans and test results
- Records about the study device

Who may use, share or receive my information?

The research team may use or share your information collected or created for this study with the following people and institutions:

- The [redacted] (IRB), a group of people who review the research study to protect your rights
- Officials of the [redacted] and
- Members of the research team, including the study doctors, research nurses and study coordinators
- Makers of the devices [redacted])
- The U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Governmental agencies in other countries

Those persons or organizations that receive your information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by the laws governing them.

Will I be able to review my research record while the research is ongoing?

No. We are not able to share information in the research records with you until the study is over. To ask for this information, please contact the Principal Investigator, the person in charge of this research study.

Do I have to give my permission?

No. You do not have to permit use of your information. But, if you do not give permission, you cannot take part in this research study. (Saying no does not stop you from getting medical care or other benefits you are eligible for outside of this study.)

If I say yes now, can I change my mind and take away my permission later?

Yes. You may change your mind and not allow the continued use of your information (and to stop taking part in the study) at any time. If you take away permission, your information will no longer be used or shared in the study, but we will not be able to take back information that has already been used or shared with others. If you say yes now but change your mind later for use of your information in the research, you must write to the researcher and tell him of your decision:

[redacted]

How long will my permission last?
There is no set date when your permission will end. Your health information may be studies for many years.

Where can you get more information?
You may call the National Cancer Institute's Cancer Information Service at:
Voice: 1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/
For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/
If you do not have access to a personal computer, you may access these websites and other information at a computer in the Resource and Learning Center on the second floor of the [redacted]

AGREEMENT TO PARTICIPATE
I have read this entire form, or it has been read to me, and I believe that I understand what has been discussed. All of my questions about this form or this study have been answered.

I agree to take part in this study.

Subject Name:_____

Subject Signature:_____ Date: _____

FOR NON-ENGLISH SPEAKING SUBJECTS:

Signature of Reader/Translator If the Subject Does Not Read English Well:

The person who has signed above, _____, does not read English well. You read English well and are fluent in _____ (*name of the language)*, a language that the subject (his/her parent(s)/legal guardian) understands well. You understand the content of this consent form and you have translated for the subject (his/her parent(s)/legal guardian) the entire content of this form. To the best of your knowledge, the subject (his/her parent(s)/legal guardian) understands the content of this form and has had an opportunity to ask questions regarding the consent form and the study, and these questions have been answered (his/her parent(s)/legal guardian).

Reader/Translator Name:_____

Reader/Translator Signature:_____ Date:_____

Witness Name:_____

Witness Signature:_____ Date:_____

Signature of Investigator/Individual Obtaining Consent:
To the best of your ability, you have explained and discussed the full contents of the study including all of the information contained in this consent form. All questions of the research subject and those of his/her parent or legal guardian have been accurately answered.

Investigator/Person Obtaining Consent:_____

Signature:_____ Date: _____