ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A221803

MEPITEL FILM FOR THE REDUCTION OF RADIATION DERMATITIS IN BREAST CANCER PATIENTS UNDERGOING POST-MASTECTOMY RADIATION THERAPY: A RANDOMIZED PHASE III CLINICAL TRIAL

Supplied product: Mepitel Film; Alliance IDE G200248

ClinicalTrials.gov Identifier: NCT04989504.

Study Chair

[redacted]

Study Co-chair

[redacted]

Study Co-Chair

[redacted]

Health Disparities Co-chair

[redacted]

Radiation Oncology Co-chairs

[redacted]

Dermatology Co-chair

[redacted]

Community Oncology Co-chair

[redacted]

Symptom Intervention Committee Co-Chairs

[redacted]

Breast Committee Co-chairs

[redacted]

Co-Primary Statistician

[redacted]

Secondary Statistician

[redacted]

Data Manager

[redacted]

Protocol Coordinator

[redacted]

Participating Organizations:
Alliance/Alliance for Clinical Trials in Oncology (lead), ECOG-ACRIN / ECOG-ACRIN Cancer Research Group, NRG / NRG Oncology, SWOG / SWOG

Study Resources:

Expedited Adverse Event Reporting

[redacted]

Medidata Rave® iMedidata portal

[redacted]

OPEN (Oncology Patient Enrollment Network)

[redacted]

Biospecimen Management System

[redacted]

Protocol Contacts:

A221803 Nursing Contact

[redacted]

A221803 Pharmacy Contact

[redacted]

Biospecimens Accessioning and Processing (BAP)

[redacted]

IROC Rhode Island

[redacted]

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

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For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at [redacted] and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at [redacted] Contact the CTSU Help Desk with any OPEN-related questions by phone or email : [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions. Do not submit study data or forms to the CTSU. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website [redacted]		
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For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or email: CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.		

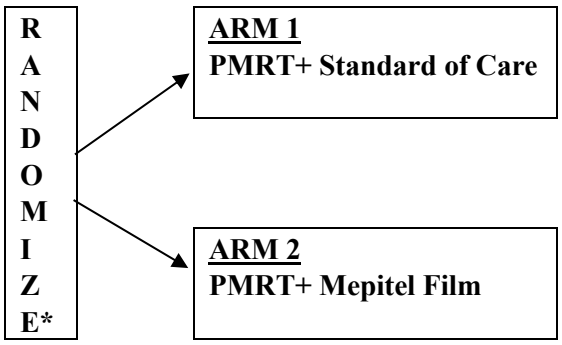
MEPITEL FILM FOR THE REDUCTION OF RADIATION DERMATITIS IN BREAST CANCER PATIENTS UNDERGOING POST-MASTECTOMY RADIATION THERAPY: A RANDOMIZED PHASE III CLINICAL TRIAL

Eligibility Criteria (see Section 3.0)

- Histologic Confirmation of breast malignancy. (See §3.2.1)
- Patients must have undergone a mastectomy with or without reconstruction. (See §3.2.2)
- No prior radiotherapy to any portion of the planned treatment site. (See §3.2.3)
- No documented history of adhesive or tape allergy. (See §3.2.4)
- Patients must be scheduled to receive conventionally fractionated photon-based radiation. Patients planning brachytherapy within the treatment field, and patients scheduled to receive bilateral radiation or hypofractionated radiation are not eligible. (See §3.2.5)
- No active rash or pre-existing dermatitis within the treatment field. (See §3.2.6)
- No co-existing medical conditions with life expectancy < 2 years. (See §3.2.7)
- No active collagen vascular diseases. (See §3.2.8)
- No concomitant cytotoxic chemotherapy. (See §3.2.9)
- No current inflammatory breast cancer, or gross dermal involvement at initiation of radiotherapy. (See §3.2.10)
- No previous history of organ or bone marrow transplant. (See §3.2.11)
- Age ≥ 18 years. (See §3.2.12)
- ECOG Performance Status 0-1. (See §3.2.13)
- Participants must be able to speak and read English. (See §3.2.14)

Required Initial Laboratory Values
None

Schema



* Patients will be randomized in a 2:1 ratio to receive either Mepitel Film or existing institutional standard of care. Post Mastectomy Radiation treatment (PMRT) is to be delivered for five to six weeks. For patients randomized to the Mepitel arm, Mepitel Film will be applied at least once every two weeks or more often if required, prior to radiation treatment. All patients will be followed for 5 years (See Section 5.0 for follow up schedule).

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Mepitel Film application should be performed at the registering institution. Radiation therapy should be delivered at the registering institution.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

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1.0 BACKGROUND

1.1 Introduction

Radiation therapy is an integral part of breast cancer treatment for many women and is associated with a unique toxicity profile. In recent years, technological improvements in radiation delivery systems have resulted in reduced doses to normal tissues.[1] However, in women requiring post-mastectomy radiotherapy (PMRT), decreasing radiation dose delivered to the skin may not be desirable because the skin is considered part of the treatment target. Indeed, in PMRT the skin is often intentionally covered with bolus to ensure coverage of the dermis and dermal lymphatics. Amongst women undergoing PMRT, radiation dermatitis continues to be a widespread source of treatment-related morbidity.[2] Acutely, radiation dermatitis manifests as moist desquamation in up to 73% of patients, grade 3+ pain in up to 32% of patients, pruritus, and nearly universal erythema.[3,4] The acute skin reaction may compromise quality of life.[5] Importantly, the acute toxicity of radiation dermatitis is correlated with the risk of long term sequelae.[6,7] Severe acute toxicity may lead to consequential chronic effects including telangiectasias, hyperpigmentation, and, in extreme cases, ulceration and necrosis.[6,8] Severe skin toxicity may also lead to incomplete or interrupted treatment, which risks compromise of the oncologic outcomes, and could increase the risk of breast reconstructive complications, including reconstruction failure.[9,10] The etiology of radiation dermatitis is incompletely understood. There is wide variation in the severity of dermatitis between patients, suggesting that the etiology of severe radiation dermatitis is more complex than the dose to the skin or the volume of skin irradiated alone. Given the potential impact on treatment related morbidity and quality of life, a better understanding of the pathogenesis of radiation dermatitis and means of preventing this important complication of PMRT is needed.

1.2 Previous studies for the prevention of radiation dermatitis

Over the years, multiple topical agents have been investigated for the prevention of radiation dermatitis, with mixed, but largely negative outcomes. Over fifty studies have reported between 1979 and 2017 examining various topical agents.[11] Despite clinical interest, most agents have not been consistently advantageous. Topical steroids have been evaluated in trials consisting mostly of whole breast radiation patients and have shown some modest efficacy. In one such trial, while improvements were noted in certain patient reported measures, there was no difference in the primary endpoint of mean maximum grade of radiation dermatitis.[12] A second randomized study, largely performed in the setting of hypofractionated whole breast radiation, demonstrated a significant reduction in radiation dermatitis, as measured by reflectance spectrophotometry, and statistical improvements in quality of life with mometasone, when compared to Diprobase.[13] However, the absolute improvement was small, with a reduction in average erythema mean score from 1.45 to 1.3, leading to some question about the clinical relevance of the reductions. A recent trial amongst women undergoing PMRT found that compared with eucerin cream, 0.1% mometasone resulted in decreased rates of moist desquamation from 66.7% to 43.8% and longer time to development of grade 3 dermatitis; however, there was no difference in patient reported outcomes.[14] Thus, while corticosteroids appear to show some impact on development of high grade dermatitis, impact on quality of life in the highest risk population is unclear, and preventive use of mometasone has not been widely adopted.

Multiple non-steroidal topical creams have been examined, with no clear improvement in dermatitis prevention. Compared with standard of care, hyaluronic acid based gel was worse than a petroleum based gel at prevention of grade 2 or higher dermatitis.[15] The twice daily application of processed ultra emu oil was also examined in a double- blind, placebo-controlled pilot study; however, no differences were noted in the primary endpoint examining radiation

dermatitis.[16] The use of topical aloe vera has demonstrated conflicting results between trials, with some trials supporting a small beneficial impact and others revealing no effect.[13,17-23] In one such trial of 225 breast cancer patients, comparing aloe vera to placebo, the use of aloe vera was associated with an increased rate of dry desquamation and pain.[24] Thus, despite the multitude of clinical trials aimed at prevention of radiation dermatitis, there is not yet one clearly efficacious strategy for reduction in risk of radiation dermatitis, leading to a variety of practices, largely based on provider preference.[25]

1.3 Rationale for current trial

Limited success with topical agents led to the investigation of silicone films for radiation dermatitis prophylaxis.[26,27] Mepitel Film is a thin, transparent, adhesive film primarily used and developed as an applied barrier in wound care.[28] A single institution clinical trial conducted in New Zealand was reported in 2014 comparing Mepitel Film and aqueous cream. The study patients were randomized between Mepitel Film coverage of the lateral or medial halves of the treatment field, with skin reaction severity compared against the uncovered portion of the field, as an internal control. This study demonstrated a significant improvement in skin toxicity with a 92% decrease in skin reaction severity, as measured by the modified Radiation Induced Skin Reaction Assessment Scale (mRISRAS). Of note, many patients included in the trial had intact breasts and underwent hypofractionated treatment which carries a lower overall risk for high grade dermatitis.[29] In addition, only 6 patients were treated with bolus and post-mastectomy patients with reconstruction were specifically excluded from this study, as well as patients that participated in prior trials evaluating the efficacy of adhesive products in decreasing radiation dermatitis.[30] Of note, Mepitel Film was recently shown to reduce moist desquamation and overall skin reaction severity in a small trial of head and neck cancer patients; a larger randomized trial (RAREST-01) to confirm these findings is ongoing.[31]

Photon radiation is inherently skin sparing. As noted above, the skin is often intentionally covered with tissue equivalent bolus material during PMRT in order to achieve therapeutically effective doses to the dermis and dermal lymphatics. Bolus may also be used to improve chest wall coverage, particularly in non-reconstructed patients with thin chests. As a result, higher skin doses are commonly delivered in the PMRT setting. Furthermore, although hypofractionation is being studied for PMRT, conventional fractionation remains the most common fractionation regimen for PMRT in North America and results in more severe skin reactions and more frequent moist desquamation.[32] Furthermore, women are increasingly electing immediate breast reconstruction following mastectomy which has important psychosocial benefits.[33,34,35] These patients are at elevated risk of radiation-induced infectious and non-infectious complications from PMRT.[36,37] Confining our patient population to PMRT patients focuses the intervention on a population with the highest risk for significant skin toxicity and associated morbidity. In contrast to PMRT, in the setting of breast conserving therapy, the skin is not intentionally treated to full dose, resulting in less significant skin toxicity. Therefore, Mepitel Film has not been systematically evaluated in the breast cancer population with the highest risk of significant dermatitis and thereby, the highest potential benefit. As such, it is important to determine the utility of thin films for prophylaxis of radiation dermatitis in post-mastectomy patients with or without reconstruction, which is the primary aim of this study.

A number of additional factors have been correlated with the degree of radiation dermatitis including BMI, race/ethnicity, and socioeconomic differences.[4,38-41] Higher rates of moist desquamation have been shown in African American women, while poor and Hispanic women have been shown to be more likely to receive a chest wall boost, placing them at high risk for more severe skin reactions.[4,38-41] Based on these data, patients with high BMI, African American women, and poor and Hispanic women in particular would be expected to gain a substantial benefit from Mepitel Film.

Importantly, the use of Mepitel Film does not result in a significant change to the radiation dose delivered to the skin or chest wall clinical target volume, as measured by thermoluminescent dosimeters and slab phantom.[42] Internal measurements conducted at Mayo Clinic suggest that because of a very small bolus effect, Mepitel Film may slightly, but clinically insignificantly, increase the skin dose. This clinically insignificant increase in dose is only observed in the first 1.67 mm of depth, beyond which there is no measurable change in dose (Appendix XI). These findings are consistent with the well understood characteristics of megavoltage photon beams used for radiation, which have an inherent skin sparing property. As such, maximum depth dose is achieved only after a "build up region" of interaction with tissue, which is why many centers apply bolus (a tissue equivalent material placed on the skin surface) to increase the superficial dose and ensure adequate treatment of the skin. Therefore, there is no physics or dosimetric rationale that would explain the diminished skin reaction with the addition of the Mepitel Film. Additionally, given there is no physical mechanism by which Mepitel Film could reduce the planned skin dose, there is no concern that Mepitel Film could detrimentally impact the oncologic efficacy of treatment.

Though the aforementioned results support the potential utility of Mepitel Film in preventing radiation dermatitis, its routine use has not been widely adapted in clinical practice. In part, this may be related to its limited availability in the US, as appropriately sized Mepitel Film is only reliably available for purchase through the Mayo Clinic Store, to the best of our knowledge. At Mayo Clinic, we conducted an initial pilot study of six post-mastectomy patients in which Mepitel was placed on half of the chest during treatment. We observed both improved physician and patient reported reductions in severity of dermatitis with Mepitel Film compared with the internal control in this small cohort (Figure 1- Appendix II). In addition, a pilot study of 33 post-mastectomy patients (20 with reconstruction), who underwent post-mastectomy radiation therapy with spot scanning intensity modulated proton therapy and Mepitel Film demonstrated that Mepitel Film is well tolerated and feasible in this patient cohort. Furthermore, 97 % of this cohort developed a maximal physician reported radiation dermatitis of grade 1-2, lower than expected from historical controls (abstract provided as Appendix I). In many cases, the boost field receiving a higher dose of radiation was covered by Mepitel Film. Though the skin in this region received a substantially higher radiation dose, the presence of Mepitel Film resulted in a lower degree of radiation dermatitis compared to the uncovered skin treated to a lower dose (Figure 2- Appendix II). We hypothesize that Mepitel Film will decrease the severity of radiation dermatitis in the intervention arm, resulting in decreased mRISRAS scores compared to the usual care arm.

In addition to determining the clinical utility of Mepitel Film for post-mastectomy patients, this study incorporates a correlative aim, designed for future investigation into the role of the skin microbiome in the development of radiation dermatitis. The mechanism of action of Mepitel Film is currently unknown. One proposed mechanism of dermatitis prophylaxis is through a reduction in friction against overlying garments or adjacent body parts.[43] A randomized study evaluating 3M Cavilon No Sting Barrier Film versus topical mometasone furoate found no difference in the rates of grade 3 dermatitis, suggesting the reduction in friction from an applied barrier is unlikely to be the only source of benefit.[44] Interestingly, Mepitel Film also serves as an antimicrobial barrier against microbes larger than 25 nm, which includes all known species of bacteria.[4] The skin microbiome is noted to be important in other inflammatory skin conditions, where dysregulation of the normal flora is a contributing factor.[45,46] Our hypothesis is that ionizing radiation disrupts the normal skin microbiome allowing opportunistic pathogens to propagate and contribute to the inflammation characteristic of radiation dermatitis, and that Mepitel Film prevents this opportunistic proliferation and thereby attenuates radiation dermatitis.

Based on our experience, Mepitel Film is well tolerated, feasible to apply in a busy clinic, and appears to reduce high grade dermatitis. A multi-institutional randomized controlled trial is needed to establish whether Mepitel Film reduces skin toxicity in patients undergoing PMRT, in order for it to become a practice standard of care. The present trial is designed to provide such information, with a correlative endpoint to evaluate a potential mechanism of action. The built-in correlative aim will yield a prospectively collected sample set from which foundational data evaluating the effects of ionizing radiation on the skin microbiome can be generated. Given the number of cancer patients across disease sites who experience radiation dermatitis, improvement in mechanistic understanding would be of great importance. Such knowledge would encourage development of future novel interventions, with the potential to alleviate one of the most common radiation associated morbidities.

1.4 Study methods

Eligible patients will be enrolled at participating institutions, and will be randomized to receive either Mepitel Film, or the existing institutional standard of care throughout the duration of their radiation. All patients will receive conventionally fractionated photon-based radiation 5 days per week for 5 weeks. A sequential boost is allowed at the discretion of the treating physician. Tissue-equivalent bolus may be applied to the chest wall during treatment to increase the skin surface dose. While radiation fractionation and boost doses will be standardized, additional radiation parameters such as CTV, PTV, skin dose, and modality (3D, IMRT, electrons) will be chosen at the discretion of the treating clinician and recorded for future analysis. A pre-treatment central review or radiation quality assurance process will not be required.

Baseline photographs utilizing standardized views from all patients and skin swabs only for those who consent to participate in the optional companion study, will be obtained prior to the start of radiation, irrespective of the randomization arm. For patients randomized to the Mepitel Film arm, baseline swabs and photographs will be obtained prior to the film application. Recommended guidelines for skin care are provided in Appendix IX in an effort to increase uniformity in the institutional standard of care arm. As specific products and/or financial support will not be provided, the skin care guidelines will remain a recommendation, rather than a requirement for participation. All products used will be recorded for inclusion in future analyses. The use of any applied prophylactic barriers aside from Mepitel Film, not including therapeutic interventions such as Xeroform, will be prohibited on this trial.

Baseline physician and patient reported surveys, including the mRISRAS, PRO-CTCAE and CTCAE toxicities will be completed prior to the start of radiation, as well as weekly while on treatment. Mepitel Film will be applied to the breast/chest wall by trained providers and changed as needed throughout treatment with a minimum frequency of once every two weeks. Based on our institutional experience, patients do not experience pain during application or removal of the Mepitel Film. Should any patient develop pain secondary to film application or removal on this study, our recommendation is to proceed with conservative management with acetaminophen or ibuprofen as needed. After completion of radiation, two additional sets of photographs will be obtained; one prior to the removal of Mepitel Film, and the second at least one hour after the removal of the Mepitel Film. These latter photographs will be used for analysis of the blinded secondary endpoint as outlined below. For patients randomized to the standard of care arm, only one set of photographs will be obtained immediately following completion of radiation therapy. A second set of skin swabs will also be obtained immediately after completion of radiation for all patients who provide their consent to participate in the optional study (following removal of the Mepitel Film for patients on the Mepitel Film arm) and all swabs will be frozen at -80°C for future analysis. The first follow-up at 7-14 days is important given the maximum degree of radiation dermatitis frequently occurs at 7-14 days post treatment. By the three-month follow-up appointment all patients would be expected to have achieved a resolution

of the acute effects of radiation dermatitis. Six-month, one year, and two-year post-treatment follow-up visits will be included to also evaluate chronic skin toxicities including telangiectasia, hyperpigmentation, skin and soft tissue fibrosis, and the rate of reconstruction failure/revision. Surveys and photographs for the assessment of acute toxicities will also be obtained at all follow-ups, whereas the chronic toxicities will be evaluated starting at the three-month follow-up.

1.5 Rationale for choosing the measurement tools

The mRISRAS is clinically validated and has been utilized in many recent studies evaluating radiation dermatitis.[26,31,42,47-49] It was specifically designed for the evaluation of radiation dermatitis, and incorporates both patient reported outcomes (PRO), and provider-scored assessments.[50,51] Alternative grading scales including the STAT, Skindex-16, and CTCAE were also considered in defining our primary endpoint; however, we chose the mRISRAS for the reasons outlined below.

The mRISRAS has a PRO component, which we think is critically important in the assessment of radiation dermatitis. Multiple provider assessment tools allow one to score the degree of erythema, desquamation, or necrosis; however, much of what patients experience when they are affected by radiation dermatitis is not externally observable. Tenderness, discomfort, pain, pruritus, burning, and the degree to which the symptoms affect the patients' day to day lives, are all metrics captured in the PRO section of the mRISRAS.

The STAT tool evaluates similar domains of burning, itchiness, pulling, and tenderness; however, patients are asked about these symptoms and the data are collected and scored by the healthcare provider.[52] This method of data collection is limited by possible confounders such as provider interpretation, variabilities in question phrasing, communication difficulties, provider bias, and the inherent impact of the patient/provider relationship. The PRO section of the mRISRAS tool, on the other hand, is specifically designed as a self-administered questionnaire. This method limits much of the possible bias of the collection method used in the PRO section of the STAT tool.

The Skindex-16 tool is an additional clinically validated tool that was also considered for analysis of the primary endpoint.[53] We have used the Skindex-16 in multiple previous Mayo NCCTG/Alliance studies successfully (MC1761, N06C4, N03CB, N05C4) and published a methodologic study on its strengths and weaknesses relative to CTCAE skin toxicity scores, with findings that recommend inclusion of both the Skindex-16 and CTCAE measures provide unique and complementary information.[53]

The strength of the Skindex-16 is that, like the PRO component of the mRISRAS, it is designed as a self-administered questionnaire.[54] For this study, the main disadvantage of the Skindex-16 is that it was developed to evaluate a variety of skin diseases and is not specific to radiation dermatitis. It also lacks any provider scored assessments, such as erythema, dry desquamation, moist desquamation, or necrosis, which are all included in the provider scored component of the mRISRAS. While the CTCAE allows for provider grading of symptoms, it is not designed as a PRO tool.

In summary, after consideration of the various assessment tools, the mRISRAS provides the strongest balance of PRO and provider assessed domains when assessing radiation dermatitis. Given the psychometric properties of the RISRAS were evaluated in 1999, as part of this study we will conduct psychometric testing of the mRISRAS.[51]

There will also be a short PRO-CTCAE questionnaire which patients will be asked to answer, along with the mRISRAS questions. The four questions are designed to evaluate radiation skin reaction, itching, general pain, and breast swelling and tenderness. The questions ask patients to

rate symptom severity using terms such as “none, mild, moderate, etc.” or symptom frequency, using terms such as, “never, rarely, occasionally, etc.” The PRO-CTCAE responses will be evaluated as exploratory analyses.

Six secondary endpoints are included in this study. The first is designed to provide a centralized, blinded, provider-assessment of the maximum severity of radiation dermatitis as measured before and after radiation therapy using the provider-scored mRISRAS. Standardized views and photograph technique details may be found in Section 6.4 and Appendix III. The degree of radiation dermatitis as scored by the separate provider-scored component of the mRISRAS, and the combined patient- and provider- scored mRISRAS are included as additional secondary endpoints. These latter two endpoints will be based on the institutionally obtained data and will provide additional context to the primary and aforementioned blinded secondary endpoint. Time to biopsy proven local and/or regional failure will also be included as a secondary endpoint. The final two secondary endpoints include the analysis of acute and chronic toxicities according to CTCAE (Version 5.0). Because the CTCAE Version 5.0 scales for telangiectasia, and hyperpigmentation are developed for total body surface area, they are inappropriate for this study. Therefore, telangiectasia and hyperpigmentation will be scored using a 4-point scale representing none, mild, moderate, and severe. The CTCAE was selected when evaluating acute and chronic toxicities, as it is the most widely used tool by clinicians in reporting symptoms. Using this may allow for better cross-study comparisons with previously conducted clinical trials. In addition, PRO surveys do not always correlate with CTCAE toxicities, and the inclusion of both analysis tools will allow for a more robust analysis of the effect of Mepitel Film on the development of radiation dermatitis.[53]

Five exploratory endpoints are included in this study. Chronic sequelae of PMRT contribute substantially to patient morbidity, and as such, two exploratory endpoints have been included to evaluate these outcomes.[55] The first captures reconstruction complications, defined as wound dehiscence, wound infection requiring the administration of oral or IV antibiotics, mastectomy skin flap necrosis, reconstructive flap necrosis not resulting in complete loss of flap, capsular contracture, or implant leakage/rupture/deflation. The second exploratory endpoint captures reconstruction failure, defined as loss of autologous reconstruction/flap, implant explantation, or unplanned expander removal without immediate replacement. The specific nature of each occurrence will be collected, though these endpoints will be scored as (yes; no). These have been included as exploratory endpoints, rather than secondary endpoints, as they will only be applicable to the subset of patients who choose to undergo post-mastectomy reconstruction.

A short PRO-CTCAE (Version 1.0) questionnaire is included to evaluate patient reported domains related to skin toxicity, including itching, radiation skin reaction, pain, and breast swelling and tenderness. The inclusion of multiple assessments allows us to determine the degree of correlation, redundancy, and uniqueness of information that each measure provides in assessing radiation-specific dermatitis. Comparative psychometric analysis of the mRISRAS will be carried out by procedures established by our statistical methods group.[56] In brief, we will carry out simple correlational analyses followed by Bland-Altman procedures after translating the measures onto a common 0-100 scale.[57] We will also carry out a responsiveness analysis using the methods of Stockler and Guyatt.[58]

In general, FDA guidance and other guidelines recommend that a general measure of well-being supplemented by a treatment/disease specific measure is optimal for obtaining a complete evaluation of a patient’s QOL. It is rare, however, that we have the opportunity to compare measures head-to-head, the preferred method for assessment comparison. Patient burden of multiple assessments is often a barrier, but in this case the brevity of each measure makes this comparison practical. The mRISRAS 4 items, and 4 PRO-CTCAE items totals to 8 items for the patient to complete, which should take no longer than five minutes and is of a size consistent

with our general approach to minimizing patient burden by restricting PRO assessments to a reasonable number of items.[59]

As discussed in Section 1.3, there is no reason to suspect Mepitel Film would impact oncologic outcomes. Nevertheless, this is an important outcome to fully evaluate, and an exploratory endpoint evaluating local and/or regional failure is also included in this study. Finally, as part of the study, we have incorporated a new survey for site staff to complete, which is designed to evaluate the performance of Mepitel Film (Appendix VIII). This survey is not a validated metric but has been designed as a quick method for nursing to track and record their experience in working with Mepitel Film. The survey tracks the frequency of film exchange, quantity of film used, incidence of film detachment, time and number of personnel required for exchange, and ease of use, allowing for descriptive reporting of these parameters. Recognizing that the application of Mepitel Film requires personnel support, demonstration of its feasibility and ease of use will provide valuable data regarding its generalizability. Furthermore, tracking the quantity of Mepitel Film used across patients will allow for an estimation of the average financial cost of this intervention.

1.6 Correlative aim

In addition to determining the clinical utility of Mepitel Film for post-mastectomy patients, this study incorporates a correlative aim designed to evaluate the role of the skin microbiome in the development of radiation dermatitis. The mechanism of action of Mepitel Film is currently unknown. Based on published data, as well as analyses conducted at Mayo Clinic evaluating the effect of Mepitel Film on the dose delivered to tissues, there is no clear physics or dosimetric rationale to explain the diminished skin reaction observed with the addition of Mepitel Film (Appendix XI).[42] The presumed mechanism responsible for its ability to attenuate the severity of radiation dermatitis has been through a reduction in friction between the affected skin and overlying garments. Interestingly, Mepitel Film also serves as an antimicrobial barrier against microbes larger than 25 nm, which includes all known species of bacteria.[60] The microbiome of the skin is increasingly recognized as important in the context of inflammatory skin conditions.[61] Reduction in skin microbiome diversity and colonization with pathogenic bacteria has been found to correlate with severity of inflammatory dermatitis.[62] Our hypothesis is that ionizing radiation disrupts the normal skin microbiome allowing opportunistic pathogens to propagate and contribute to the inflammation characteristic of radiation dermatitis, and that Mepitel Film prevents this opportunistic proliferation thereby attenuating radiation dermatitis. See Section 14.1.

1.7 Accrual plan

This trial is well suited to a multi-institutional approach. The generalizability of the outcomes to both academic and community cancer centers would be strengthened by demonstrating a successful intervention across diverse populations and multiple centers. Though substantial interest has been demonstrated through a feasibility survey sent to Alliance Community Oncology Committee members, ensuring adequate accrual is central to the success of a multi-institutional trial. As such, our accrual plan includes a focus on providing direct support for participating sites, as well as outreach through a number of different channels to boost recruitment of interested sites.

For participating sites, the study team will be available to address questions as needed either via email or phone. Training sessions will be provided at the twice-yearly Alliance meetings and the study team will be available to address questions as needed.

In addition to Alliance participation, we will advertise among NCTN groups, including SWOG, NRG Oncology, and ECOG-ACRIN, with a particular focus on directly contacting member

radiation oncologists who may be interested in participating. We will also advertise through direct networking at radiation oncology specific meetings, such as the American Society for Radiation Oncology (ASTRO) annual meeting. Social media has also become an increasingly important venue for dissemination of information and targeted information regarding the trial will be posted to relevant sites, such as [redacted] which is a radiation oncology specific network. Finally, we will work to have our trial cross-referenced in appropriate, active Radiation Oncology protocols.

Importantly, given this trial relies on participation of radiation oncologists, we will ensure that our outreach highlights a few important aspects of Mepitel Film; namely it has thus far shown to be well tolerated, is feasible to incorporate into a busy clinic, and does not result in a significant change to the radiation dose delivered to the skin or chest wall.

2.0 OBJECTIVES

2.1 Primary objective

To determine the ability of Mepitel Film to reduce the severity of radiation dermatitis in patients undergoing post-mastectomy radiotherapy for breast cancer when compared to the institutional standard of care.

2.2 Secondary objectives

2.2.1 To determine the ability of Mepitel Film to prevent radiation-induced dermatitis based on a centralized, blinded provider assessment review of photographs.

2.2.2 To determine the ability of Mepitel Film to prevent radiation-induced dermatitis based on a non-blinded institutional provider assessment.

2.2.3 To determine the ability of Mepitel Film to prevent radiation-induced dermatitis based on a combined patient and non-blinded provider assessment.

2.2.4 To evaluate time to local and/or regional failure.

2.2.5 To determine the frequency and severity of acute adverse events.

2.2.6 To determine the frequency and severity of chronic radiation therapy-related adverse events including skin and soft tissue fibrosis, telangiectasia, and hyperpigmentation.

2.3 Exploratory objectives

2.3.1 To determine the ability of Mepitel Film to decrease the rate of reconstruction complications**.**

2.3.2 To determine the ability of Mepitel Film to decrease the rate of reconstruction failure.

2.3.3 To determine the number of Mepitel Film changes required during treatment, evaluate ease of use from a nursing perspective, and estimate financial cost of the intervention.

2.3.4 To determine the frequency and severity of patient-reported itching, radiation skin reaction, pain, and breast swelling and tenderness.

2.3.5 To determine the long-term severity of radiation dermatitis, as measured by the combined patient- and provider-completed mRISRAS scores obtained at 6-months, 1-year, and 2-years post-radiation therapy.

2.3.6 To conduct psychometric testing of the mRISRAS**.**

2.4 Correlative science objective

2.4.1 To obtain skin swabs for future analysis of the impact of ionizing radiation and Mepitel Film on the skin microbiome and *Staph aureus* through 16S deep sequencing and targeted droplet digital polymerase chain reaction and/or quantitative PCR, respectively.

3.0 PATIENT SELECTION

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

3.1 On-Study Guidelines

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

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

- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.

In addition:

- Women of reproductive potential should agree to use an appropriate method of birth control throughout the duration of radiation due to the teratogenic potential of the radiation utilized in this trial.
- Patients must be available to initiate thin film usage before the start of radiation (same day or earlier), if randomized to the Mepitel Film arm.

3.2 Eligibility Criteria

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

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

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.2.1 Documentation of Disease: Histologic Confirmation of breast malignancy with TNM staging.**

___ **3.2.2 Patients must have undergone a mastectomy with or without reconstruction** within the past 120 days if not receiving adjuvant therapy, or within 60 days after completion of the last dose of chemotherapy.

___ **3.2.3 Prior Treatment: No prior radiotherapy** to any portion of the planned treatment site**.**

___ **3.2.4 No documented history of adhesive or tape allergy.**

___ **3.2.5 Patients must be scheduled to receive conventionally fractionated photon-based radiation.** Patients planning brachytherapy within the treatment field, and

patients scheduled to receive bilateral radiation or hypofractionated radiation are not eligible.

___ 3.2.6 No active rash or pre-existing dermatitis within the treatment field.

___ 3.2.7 No co-existing medical conditions resulting in life expectancy < 2 years.

___ **3.2.8 Comorbid conditions:** No active collagen vascular diseases (i.e. lupus erythematosus, scleroderma, dermatomyositis).

___ **3.2.9 Concomitant medications:** No concomitant cytotoxic chemotherapy. However, treatment with T-DM1 is allowed. In addition, endocrine therapy, CDK 4/6 inhibitors, pembrolizumab, and other HER2 directed therapies are also allowed.

___ 3.2.10 No current inflammatory breast cancer, or gross dermal involvement at initiation of radiotherapy.

___ 3.2.11 No previous history of organ or bone marrow transplant.

___ 3.2.12 Age ≥ 18 years.

___ 3.2.13 ECOG Performance Status 0-1.

___ **3.2.14 Language:** In order to complete the mandatory patient-completed measures, participants must be able to speak and read English.

___ 3.2.15 Required Initial Laboratory Values: None

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at [redacted]Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

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

Refer to the [redacted] for additional information. For questions, please contact the **RCR Help Desk** by email at [redacted]

4.2 CTSU Site Registration Procedures

This study is supported by the NCI CTSU.

IRB Approval:

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

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

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

4.2.1 Additional site registration requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (U.S. sites only); and

- Compliance with all applicable protocol-specific requirements (PSRs).

4.2.2 Protocol Specific Requirements for A221803 Site Registration

- **IROC credentialing:**

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

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

To complete protocol-specific credentialing the RTI provider or enrolling site should follow instructions in the protocol to submit documentation or other materials to the designated IROC Quality Assurance (QA) center. Upon the IROC QA center approving the RTI provider for the study modality, IROC will send the institution a credentialing letter via email. The institution will need to upload the letter to the Regulatory and Roster Maintenance applications to comply with the protocol specific requirement.

Upon site registration approval in the Regulatory application, the enrolling site may access Oncology Patient Enrollment Network (OPEN) to complete enrollments. If the study is using the IROC integration suite, the enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist.

Site Approval form.

Submission of the Site Approval Form is required at the time of site registration. (See Section 15.0). The Site Approval Form must be submitted as indicated in Section 4.2.4.

Mepital Film Online Video Training.

Site personnel are required to watch the Mepitel Film application training video on CLASS and be familiar with the application process prior to ordering supplies. See section 15.3 for instructions).

4.2.3 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website [redacted]

- Click on *Protocols* in the upper left of the screen:
  - Enter the protocol number in the search field at the top of the protocol tree, or

- Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number [*A221803*].

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

4.2.4 Submitting Regulatory Documents

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

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

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] to receive further instruction and support.

4.2.5 Checking Your Site's Registration Status

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

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

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

4.2.6 Credentialing

See Section 15.0 for credentialing requirements.

4.2.7 Delegation of Task Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

4.3 Patient Registration Requirements

Informed consent: The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature

of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patient completed booklets: Patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient completed booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A221803 CTSU site) and submitting it through the CTSU regulatory portal. Samples of the booklets are found in Appendices VI -VII, which are to be used for reference and IRB submission only. They are not to be used for patient completion.

This study includes the use of the mandatory patient completed measures, mRISRAS and PRO-CTCAE. The mRISRAS is available in English. Participation in Alliance A221803 is restricted to patients who are able to speak, understand and read this language.

Protected Health Information: In order to conduct the exploratory analyses for this study, it will be necessary to collect the following information from all participants:

1) Birth Date
2) Ethnicity and race
3) Zip code + 4

This information will be collected on the Demography form in Medidata Rave and stored with the study data to be used for the analysis.

4.4 Patient Registration/Randomization Procedures

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

Requirements for OPEN access:

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

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

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

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

- Staff involved in Mepitel Film application have reviewed resources as outlined in Section 15.1.

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

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

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

4.5 Registration to Correlative and Companion Studies

4.5.1 Registration to Substudies described in Section 14.0

There is one substudy within Alliance A221803. This correlative science study must be offered to all patients enrolled on Alliance A221803 (although patients may opt to not participate). This substudy does not require separate IRB approval. The substudy included within Alliance A221803 is:

- **The Impact of Ionizing Radiation and Mepitel Film on the Skin Microbiome, Alliance A221803-ST1**

If a patient answers "yes" to "My samples and related information may be used for the additional studies described above," Question #1 in the model consent, "I agree that my samples and related health information may be used for the laboratory study described above", they have consented to participate in the substudy described in Section 14.1. The patient should be registered to Alliance A221803-ST1 at the same time they are registered to the treatment trial (A221803). Samples should be submitted per Section 6.2.

4.6 Stratification Factors

The randomization routine is found in Section 13.0 (Statistical Considerations). All eligible subjects will be stratified by:

4.6.1 Breast reconstruction (yes versus no)

4.6.2 Planned boost (yes versus no)

4.6.3 Planned bolus (yes versus no)

4.6.4 BMI <25.0 versus 25.0-29.99 versus ≥ 30.0

4.7 Treatment Assignments

After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the 2 treatment groups using the dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups.

Patients will be randomized in a 2:1 ratio, favoring the intervention group, to receive:

- Intervention group: Mepitel Film throughout the duration of their radiation

- Control Group: The existing institutional standard of care throughout the duration of their radiation.

5.0 STUDY CALENDAR

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

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

To be completed ≤ 28 DAYS before registration: History and physical.

	Prior to Registration	Every week, prior to RT	7-14 days post RT	3 months, 6 months, 1 year, and 2 years post RT*	Months 30, 36, 42, 48, 54, 60 months post RT
Tests & Observations					
History & Physical (H&P), weight, height, ECOG PS	X	A		B	B
Acute Toxicities & AE Assessment		X (1)	X (1)	X (1)	
Photographs		C (2)	X (2)	X (2)	
Skin Care Form (App. IV)		X (3)	X (3)	X (3)	
Chronic Toxicities & AE Assessment				X (1)	
Recurrence Assessment				X (4)	
Laboratory Studies					
Serum or Urine HCG		D			
Questionnaires					
mRISRAS (App.VI-patient and provider completed)		X	X	X	
PRO-CTCAE (App. VII)		X	X	X	
Thin Film Clinical Utilization Survey (App. VIII-Site staff completed)		X			
Correlative Study Skin Swabs	*For patients who consent to participate, See Section 6.2 for submission instructions and time points*				

* +/- 6 weeks, except for 3 months post RT, +/-2 weeks

1 AE assessment includes both CTCAE and non-CTCAE items, See Section 9.1 and Section 9.2.1 for list of AEs and Appendix V for attribution related to non-CTCAE items.

2 See Section 6.4, Section 11.3 and Appendix III.

3 Completed by site personnel who apply Mepitel Film, See Appendix IV.

4 See Sections 6.1.3 and 11.5

A Prior to week 1 only. H&P does not need to be repeated if done within the past 60 days.

B Physical exam to evaluate local recurrence is required every 3 months for 1 year and every 6 months (+/- 30 days) from years 2-5 post RT. For years 3 through 5 (months 30 through 60), physical exams may be performed by the patient's local health care provider.

C Initial photographs are to be acquired prior to the first application of Mepitel Film and no more than 3 days prior to the start of radiation therapy.
Post-treatment photographs should be acquired upon completion of radiation and prior to removal of Mepitel Film **and** after a minimum of one hour following removal of Mepitel Film.

D For women of childbearing potential. Must be done within 2 weeks prior to start of RT.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule:

A Data Submission Schedule (DSS) is available on the Alliance study webpage, within the Case Report Forms section. The Data Submission Schedule is also available on the CTSU site within the study-specific Case Report Forms folder.

6.1.2 Medidata Rave

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

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

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

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

Upon initial site registration approval for the study in, the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management > Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata

screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

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

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.3). Samples of questionnaire booklets are available in Appendices VI-VII for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff either in person or by mail and site staff will enter patient and caregiver responses into Rave.

6.1.3 Supporting Documentation to be Submitted to the Alliance

This study requires supporting documentation to be submitted through Medidata Rave at the following timepoints:

Baseline: Pathology from mastectomy, all operative notes, and any notes documenting post-operative or reconstruction related complications.

2 years post RT: All pathology reports and radiology/imaging reports obtained from enrollment through the 2 year post RT follow-up must be submitted to assess recurrence.

6.1.4 Data Quality Portal

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

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

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data using a direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

6.2 Specimen collection and submission

For patients registered to substudy A221803-ST1: Skin swab samples will be obtained before and after radiation therapy. All participating institutions must ask patients for their consent to participate in the correlative substudies planned for Alliance A221803-ST1, although patient participation is optional (see Section 6.2.2).

Rationale and methods for the scientific components of this study are described in Section 14.0. For patients who consent to participate, skin swabs will be collected at the following time points for this study:

	Prior to RT	At completion of RT	Storage/ Shipping conditions	Submit to:
For patients registered to A221803-ST1, submit the following: (optional)				
Number of samples to collect:				
Skin swabs (1)	8 swabs*	8 swabs*	Frozen	Mayo BAP Freezer

* See Section 6.2.2 and Appendix X for detailed collection instructions

1 Skin microbiome analyses described in Section 14.1

6.2.1 Specimen Submission Using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: [redacted] using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted] For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

Sample collection kits must be ordered thought BIOMS. Please log into BioMS and click on "Kit Requests" to order Skin swab collection kits.

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (A221803), Alliance patient number, patient's initials, date of procurement and type of specimen collected (e.g., skin swabs), as well as the code specifying location of sample (e.g. S-1, S-2, etc. – see Appendix X).

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

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

Ship specimens Monday through Friday frozen on dry ice, overnight. Do not ship specimens on Saturdays.

Batch shipments are not allowed. **Specimens must be frozen within 2 hours of collection and shipped the same day as collection.** All samples should be shipped frozen. Avoid freeze-thaw cycles. Samples will be placed in long term storage at -80°C upon receipt by the Alliance Biorepository at Mayo Clinic.

All specimens should be sent to the following address:

[redacted]

6.2.2 Swab collection Procedures

For all patients who consent to participate, (model consent question, "I agree to have my specimen collected and I agree that my specimen sample and related information may be used for the laboratory study described above"), skin swab samples will be used for the microbiome studies described in Section 14.1. These samples should be collected prior to the initiation of radiation treatment and at completion of radiation treatment. Samples should be obtained as detailed below and in Appendix X and shipped frozen according to Section 6.2.1.

Label samples with the following identification:

1) Procurement date/time of collection

2) Alliance patient number

3) Patient initials

4) Alliance study number (i.e., A221803-ST1)

Preparing for swab collection for patients on the standard of care arm:

1. Make sure to review which side will be receiving treatment (right vs left). Review patient randomization to confirm patient is randomized to institutional standard of care arm. Please see Appendix X and follow instructions during collection of skin swabs.
2. Collect swabs as directed in Appendix X.

Preparing for swab collection and Mepitel Film application for patients on the Mepitel Film arm:

3. Make sure to review which side will be receiving treatment (right vs left). Review patient randomization to confirm patient is randomized to receive Mepitel Film. Please see Appendix X and follow instructions during collection of skin swabs, and Mepitel Film application.
4. Mark the skin with non-permanent marker to outline area where the Mepitel Film will be placed. These marks will help ensure the swabs are collected from the

correct areas of skin. Mark the contralateral breast/ chest wall where the small control square of Mepitel Film will be placed.

5. Collect swabs as directed in Appendix X.

Swab collection technique:

Equipment:

- 8 swabs
- Sterile Gloves
- 1 pre-filled sterile saline syringe

Collection:

1. Arrange patient in comfortable treatment position with skin exposed.
2. Arrange tubes.
3. Arrange diagram for guidance.
4. Open sterile gloves and use paper for semi-sterile field.
5. Open syringe and expel small amount of saline to get it started.
6. Open first swab, moisten tip with 4-5 drops sterile saline.
7. Shake swab gently to eliminate excess saline.
8. Hold pre-moistened swab at approximately 45-degree angle to the skin and swipe area with 20 swipes (one swipe = one direction back and forth would equal two swipes, so 20 swipes is equal to 10 back and forth swipes). Swipe length should be approximately 5 cm. Use firm, even pressure. The swab tip is fairly flimsy, so it will only allow a certain amount of pressure. Most importantly, keep pressure and swab technique uniform across swab collections and across patients.

   ** Please note that when collecting final swabs, the intended collection area may be affected by moist desquamation. In these cases, collect the skin swab from the immediately adjacent intact skin, rather than directly from the area of moist desquamation. In cases of moist desquamation, also collect a 9th swab from the area of moist desquamation. In severe cases, omitting a particular skin swab is allowed at the discretion of the investigator.
9. Re-cap swab in tube, and double check it is appropriately labeled.
10. Repeat #6-9 until all 8 swabs are collected.
11. Transfer tubes into -20°C freezer or dry ice within 2 hours of collection.

    Please note: All 8 swabs collected from the same patient at the same time point should be placed in one biohazard bag and shipped according to IATA guidelines on sufficient dry ice by overnight mail to the Alliance Biorepository at Mayo Clinic. (Section 6.2.1)
12. Samples should be mailed on dry ice same day, overnight. Avoid freeze thaw cycles. Samples will be accessioned into the Alliance Biorepository at Mayo Clinic (Mayo BAP) for long term storage at -80°C.

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

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

6.3.1 TRIAD Access Requirements

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

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

6.3.2 TRIAD Installations

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

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

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

6.3.3 Procedures for Data Submission via TRIAD

Radiation therapy treatment plan digital data must include CT scans, structures, plan, and dose files. This study uses TRIAD for submission of RT data. Use of TRIAD requires several preliminary steps as described in Section 6.3.1 and 6.3.2..

Additional information is available at:

[redacted]

6.4 Submission of photographs for assessment of acute and chronic toxicities

Photographs of the chest wall will be captured utilizing standardized views (Appendix III). Baseline photographs will be obtained **from all patients** prior to the start of radiation, irrespective of the randomization arm. **For patients randomized to receive Mepitel Film,** baseline photographs will need to be acquired prior to the placement of Mepitel Film. After completion of radiation, two additional sets of photographs will be obtained; one prior to the removal of Mepitel Film, and the second at least one hour after the removal of the Mepitel Film. Photographs for assessment of acute and chronic toxicities will also be obtained at all follow-up time points: 7-14 days post treatment, 3 months, 6 months, 1 year and 2 years post-treatment.

The photographs should be in an image format, such as .jpg. Scanned photographs will not be accepted. See Section 11.3 and Appendix III for photography instructions.

Deidentified photographs will be submitted via email to [redacted] Please put the protocol number and patient's study ID in the subject line of the email. Alternatively,

photographs can be submitted via TRIAD. See Section 6.3 for instructions for submission via TRIAD.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 6 weeks of registration.

For questions regarding treatment, please see the study contacts page.

Radiation therapy may begin no sooner than 21 days after surgery, or 14 days after the completion of chemotherapy.

Chemotherapy is defined as cytotoxic chemotherapy, not biological therapy, such as trastuzumab, pertuzumab, etc.

Randomization: Patients will be randomized to either standard of care, or Mepitel Film. Patients receiving standard of care will receive skin care according to their institutional standard of care, as directed by their treating provider. Patients randomized to Mepitel Film, will have Mepitel Film applied to the skin within the radiation treatment field for the duration of radiation therapy.

Schedule deviations of ≤ +/- 1 day of schedule will not be considered a protocol violation.

Protocol Summary: Protocol therapy will consist of conventionally fractionated photon-based post mastectomy radiation therapy +/- a standard radiation boost, and +/- tissue equivalent bolus. Skin management will be randomized between the institutional standard of care, or Mepitel Film, which is a clear, thin, adhesive barrier that will be applied to the skin within the treatment field throughout the duration of radiation therapy.

7.1 Surgical Management

Patients are required to have undergone mastectomy, which includes a total, simple, skin sparing, nipple sparing, or modified radical mastectomy. Mastectomy may be conducted at a non-registering institution. Patients with or without reconstruction are allowed to participate in this trial. This includes immediate or delayed reconstruction, including placement of tissue expanders, allograft, saline, silicone, or autologous tissue flap. This protocol does not stipulate lymph node management, though they should be evaluated and treated according to standard of care, which may be conducted at a non-registering institution. Patients will be recorded as having undergone a sentinel node only procedure or axillary dissection. A sentinel node procedure will be considered an axillary dissection if more than 5 lymph nodes are removed. Positive margins are allowed on this study, though the extent and location should be provided.

7.2 Mepitel Film/standard of care treatment

Patients will be randomized in a 2:1 ratio to receive either Mepitel Film, or the existing institutional standard of care throughout the duration of their radiation. Radiation and protocol directed skin care (standard of care vs Mepitel Film) will be conducted at the registering institution.

7.2.1 Institutional Standard of Care Arm

Patients randomized to the standard of care arm will commence with conventionally fractionated PMRT, with skin management according to their institutional standard of care. Currently, there is no clear standard of care for reducing radiation dermatitis, and clinical practice varies widely across institutions. Patients randomized to this arm, should receive skin management as recommended by their treating physician. To help increase uniformity in the institutional standard of care arm, recommended guidelines for skin care are provided in Appendix IX. We recommend following these guidelines; however, it is not required for participation on this study. Specific skin care products will not be provided for the standard of care arm. Common interventions such as aqueous creams, petroleum ointments, aloe vera, acetic acid soaks, prescription interventions such as mometasone or lidocaine, and

wound care interventions such as Xeroform gauze or silvadene are all permitted. All products used throughout treatment will be recorded for future analyses (Appendix IV). The use of any applied prophylactic barriers including, but not limited to Mepitel Film, Mepitel One, Tegaderm, or Cavilon no sting Barrier Film, is prohibited on this trial. Therapeutic barrier interventions, such as Xeroform, are permitted to treat moist desquamation.

Acquisition of photographs is required for all patients and skin swabs (only for those who provide consent to participate in the optional sub-study). Both initial photos for all patients and skin swabs (for those who consent to participate in the optional correlative substudy) should be acquired no more than 3 days prior to the start of radiation therapy. Immediately upon completion of radiation therapy, the first set of post-treatment photographs and the second set of skin swabs should be acquired.

7.2.2 Mepitel Film Arm

Patients randomized to the Mepitel Film arm will have Mepitel Film applied to the breast/chest wall prior to starting radiation therapy and changed as needed throughout treatment with a minimum frequency of once every two weeks. The Thin Film Clinical Utilization Survey must be completed once per week prior to radiation treatment (Appendix VIII). Mepitel Film should be replaced if it peels to the point that it compromises the intended skin coverage or becomes loosely adhesive during treatment. An initial generous application of Mepitel Film can allow one to trim edges off as they peel without compromising coverage. Additionally, if only a small piece of the Mepitel Film falls off, or peels, then a person can replace only the compromised area using a patchwork technique. Importantly, a small piece of Mepitel Film will be applied to the contralateral breast/chest wall as a control. This piece should be changed as needed throughout treatment with a minimum frequency of once every two weeks.

The acquisition of photographs for all patients, and skin swabs (only for those who provide consent to participate in the optional sub-study) requires coordination with the planned placement of Mepitel Film. The initial photographs and skin swabs are acquired prior to the first application of Mepitel Film. Both initial photos for all patients and skin swabs (for those who consent to participate in the optional correlative substudy) should be acquired no more than 3 days prior to the start of radiation therapy. Mepitel Film should then be applied to the entire breast/chest wall and changed as needed throughout treatment. Upon completion of radiation the first set of post-treatment photographs should be acquired. The Mepitel Film should then be removed, and the second set of skin swabs should be acquired immediately following removal of the Mepitel Film. A minimum of one hour should pass following removal of Mepitel Film, to allow for transient erythema to resolve, before a second set of post-treatment photographs is acquired. After this second set of photographs, Mepitel Film should be reapplied to the breast/chest wall. Given radiation dermatitis can often peak in the 1-2 weeks post-treatment, this final application of Mepitel Film continues to be protective. It should be communicated to the patient, that she can allow this final layer of Mepitel Film to peel off naturally.

Step-By-Step Instructions for the Placement of Mepitel Film:

Mepitel Film may be applied by nursing support, or trained staff. Application is easiest with two individuals, though possible with one.

Patient should be positioned supine with arms up, similar to the way they are positioned for treatment.

Skin should be clean, free of lotions at the time of film placement. If needed skin can be cleansed with water only. Please do not use baby wipes, or soap to clean the skin.

Determine size of Mepitel Film needed prior to beginning application.

Pre-cutting the Mepitel Film to the appropriate size will facilitate ease of placement. It is often easier to cut one large film into two halves to have better adherence to the skin and contours of the breast.

If applying with two people, position one person on each side of the patient/exam table.

Carefully remove the backing from the Mepitel Film. Avoid allowing it to stick to itself (which it has a tendency to do).

Place one end of the film onto the patient's skin while holding the opposite end up, avoiding contact with the skin. Slowly press the film onto the patient's skin starting from the applied end working toward the opposite end. Care should be taken to work slow, cover every contour, and avoid any air bubbles under the film.

After film is applied, remove the paper border taking care to press down edges of the film as the border is removed.

Remove any air bubbles using your fingertips to work the bubbles to the edge of the film.

Tips for covering reconstructed breast: If the film is going to crease or is causing an overlap, cutting "darts" in at the corners allows the film to lie flat.

Overlap when seaming two pieces of Mepitel is acceptable and may be preferred so that seams do not come apart creating an open seam. Minimize overlap to less than 1 cm.

While showering with Mepitel in place, recommend draping a hand towel over the patient's ipsilateral shoulder, so the water does not beat directly on the Mepitel Film. Encourage patient not to shower for 24 hours after placement, to increase likelihood of adherence.

Of note, the small piece of Mepitel Film applied to the contralateral side should extend posteriorly enough that the swinging of the patient's arm does not cause the posterior border to roll up. This is generally well accomplished with a single, uncut small piece.

Optional: Immediately following placement of the film, a warm blanket may be applied over Mepitel Film field and allowed to stay in place for 2-3 minutes. This may help with adherence and bring other unseen air bubbles to the surface.

Mepitel Film is typically applied using a patchwork approach. Based on the Mayo institutional experience, patients do not experience pain during application or removal of the Mepitel Film. If, after application of the Mepitel Film, the patient develops worsening pruritus or rash that, in the treating provider's opinion, is inconsistent with radiation related toxicity, and consistent with a film intolerance or allergy, the Mepitel Film may be removed. This is an unusual occurrence affecting less than 10% of patients, and typically happens within the first week following application. These patients should then be treated according to the institutional standard of care, and the film removal documented (see on-study form in Medidata Rave). Should any patient develop pain secondary to film removal on this study, our recommendation is to proceed with conservative management with acetaminophen or ibuprofen as needed. If a patient develops moist desquamation under the Mepitel Film, the area of film immediately overlying the affected area of skin may be removed, and the treating provider should direct treatment of the moist desquamation according to their institutional standard of care. Mepitel Film should not be reapplied to

this area; however, it should remain in place over the remainder of the skin that is not affected by moist desquamation.

7.3 Radiotherapy

All radiation specific parameters should be recorded on the dosimetry form and submitted to IROC Rhode Island. Radiation will be conducted at the registering institution.

Dose: All patients will receive conventionally fractionated photon-based radiation. Acceptable regimens include:

a) 50 Gy (2 Gy per fraction x 25 fractions)

b) 50.4 Gy (1.8 Gy per fraction x 28 fractions)

Volumes: Primary treatment volumes should include the chest wall or reconstructed breast. Specific parameters defining the GTV, CTV, and PTV volumes are not defined in this trial, should be defined by the treating provider. Inclusion of the supraclavicular fossa, and/or axilla and/or internal mammary nodal basin is typical in the post mastectomy radiotherapy setting. Nodal radiation volumes and coverage are left up to the discretion of the treating physician.

Organs at Risk (OAR): Skin is the single **required** defined OAR volume included on this trial. The skin contour should be designated as a 3mm extraction from the external body contour. The D1cc, V105, and V110 of the skin must be reported.

Modality: Acceptable modalities include:

a) 3D-CRT

b) IMRT (see Section 15.1.2)

c) Hybrid 3D + IMRT

Energy: Megavoltage photon beam energies ≥ 4MV are required. Electron beams require megavoltage energies. Proton therapy is not allowed on this trial.

Boost: The use of a sequential radiation boost to the chest wall, lymph nodes, or both, is allowed on this trial, provided it complies with the following parameters:

Dose: 10-16 Gy (1.8 Gy or 2 Gy per fraction)

Modality: Photons or Electrons

Bolus: The use of tissue equivalent bolus is allowed on this trial. The specific bolus technique is directed by the treating physician according to the institutional standard of care.

Simulation: A treatment planning CT following mastectomy and immediate reconstruction (if applicable), in the treatment position is required to define organs at risk (OAR). Simulation and treatment must be performed with the patient positioned in the supine position. Acceptable immobilization includes, but is not limited to, breast boards, alpha cradle, vac loc, wing boards.

Reconstruction considerations: For patients with fluid filled expanders in place at the time of radiation planning, the amount of fluid is at the discretion of the treating physician; however, the volume should remain constant throughout radiation. If a contralateral expander is in place at the time of simulation, it may be deflated at the discretion of the treating physician; however, the volume of the contralateral expander should not change during the course of planning and radiation if it impacts doses to the treatment volumes or OAR.

7.3.1 Radiation Therapy Quality Assurance

A pre-treatment central review or Radiation Therapy Quality Assurance process is not required. Submission of treatment plans via TRIAD as DICOM RT is required within 7

days following the completion of radiation therapy. Use of TRIAD requires several preliminary steps (see Section 4.2 and Section 6.3). Additional information is available at:

[redacted]

All data should be submitted by the 7-14-day follow-up visit.

Within one week of the completion of radiotherapy, the following data should be submitted for review:

- RT treatment plan including CT, structures, dose, and plan files. These items are included in the digital plan.
- Digitally reconstructed radiographs (DRR) for each treatment field. Submission of DRR's is not required for IMRT.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
- RT-1 Dosimetry Summary Form
- The RT-2 Radiotherapy Total Dose Record Form
- A copy of the patient's radiotherapy record including the prescription, and the daily and cumulative doses to all required areas.

Any items listed above that are not part of the digital submission may be included with the transmission of the digital RT data or submitted separately via e-mail to [redacted]

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

[redacted]

Compliance Criteria

Specified Radiation Dose

Variation Acceptable: Total dose or dose per fraction is >5% but <10% of the specified protocol dose.

Deviation Unacceptable: Total dose or dose per fraction deviates by more than 10% from the specified protocol dose.

8.0 DOSE AND TREATMENT MODIFICATIONS, UNBLINDING

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Ancillary Therapy

Patients should not receive any other treatment which would be considered treatment for the primary neoplasm or impact the primary endpoint, other than endocrine treatment or HER2 directed therapies as allowed in Section 3.2.9.

8.1.2 Supportive Care

Patients should receive full supportive care while on this study. Patients randomized to the standard of care arm may use any topical intervention the treating provider deems appropriate, including, but not limited to aqueous creams, petroleum ointments, aloe vera, acetic acid soaks, prescription interventions such as mometasone or lidocaine, and wound care interventions such as Xeroform gauze or silvadene. All products used should be recorded (see Appendix IV).

Patients randomized to the Mepitel Film arm, should not apply any of the aforementioned products over the area where Mepitel Film is in place. For areas of adjacent skin not covered by Mepitel Film, any of the aforementioned products may be applied, and should be recorded (see Appendix IV). If, during the course of treatment, the Provider deems it medically necessary to remove the Mepitel Film, or if the patient is experiencing unacceptable adverse events or intolerance requiring the removal of Mepitel Film, full supportive care is recommended at the direction of the treating physician. This includes, but is not limited to, any of the aforementioned products.

Any patients who require oral medications for pain, should be offered appropriate symptom management according to their treating physician.

Any barrier films intended to be used prophylactically, in a similar manner to Mepitel Film, (i.e. Mepitel One, Cavilon no sting Barrier Film, etc.), are not allowed on this study. This does not include barriers used in the treatment of symptomatic dermatitis, such as Xeroform gauze, which are allowed for symptom management.

8.1.3 Radiation Dose and Treatment Modifications

CTEP- AERS reporting may be required for some adverse events (See Section 9.0)

PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol-directed action.

Radiation doses should not be modified. Compliance with the protocol will require acceptable radiation modalities and conventionally fractionated treatments, as defined in Section 7.0. Patients may occasionally require treatment breaks; however, Mepitel Film should not be removed during these treatment breaks, and breaks should be kept to a minimum. Treatment breaks up to 5 treatment days will be considered acceptable. Treatment breaks greater than 5 treatment days are considered unacceptable and should be strongly discouraged.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at [redacted] Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

Clinician graded CTCAE is the AE safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items, but no protocol directed action will be taken. The specific PRO-CTCAE items for this protocol can be found in Appendix VII. PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting.

9.1 Routine Adverse Event Reporting

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

Solicited Acute Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded at baseline, weekly while on treatment, at the 7-14-day post-treatment follow-up, and at the 3-month, 6-month, 1 year and 2-year post-treatment follow-up visits by CTCAE v5.0.

CTCAE v5.0 Term	CTCAE v5.0 System Organ Class (SOC)	PRO-CTCAE term
• Dermatitis radiation	• Injury, poisoning and procedural complications	• Itching
• Rash acneiform	• Skin and subcutaneous tissue disorders	• Radiation skin reaction
• Rash maculo-papular	• Skin and subcutaneous tissue disorders	• General pain
• Pruritus	• Skin and subcutaneous tissue disorders	• Breast swelling and tenderness
• Skin infection	• Infections and infestations	

Symptomatic Adverse Events reported by patients through PRO-CTCAE are not safety reporting and may be presented with other routine Adverse Event data.

Solicited Chronic Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded at the 3-month, 6-month, 1 year and 2-year post-treatment follow-up visits by CTCAE v5.0.

CTCAE v5.0 Term	CTCAE v5.0 System Organ Class (SOC)
• Superficial soft tissue fibrosis	• Musculoskeletal and connective tissue disorders
• Fibrosis deep connective tissue	• Musculoskeletal and connective tissue disorders

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs). Attribution may be secondary to radiation, and/or Mepitel Film.

Of note, pruritus is a common acute toxicity observed secondary to radiation and can also develop in response to Mepitel Film. Based on Mayo institutional experience, pruritus due to Mepitel Film is generally seen within the first week of use.

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

a) Acute Adverse Events: Other CRF - Applies to AEs occurring between registration and within 90 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Chronic Adverse Events: Late CRF - Applies to AEs occurring greater than 90 days after the patient's last treatment date.

9.2.1 Non CTCAE Adverse Event Reporting

Because the CTCAE v5.0 does not adequately characterize telangiectasia and hyperpigmentation with respect to the limited field of skin treated on this study, these AEs will be scored using a 4-point scale representing none, mild, moderate, and severe, and recorded separately. Additionally, reconstruction failure and reconstruction complications will be recorded be recorded separately from CTCAE toxicities and are integral to the pre-specified secondary endpoints (see Appendix V).

List of non-CTCAE events:

1) Telangiectasia (involving skin within radiation treatment field)
2) Hyperpigmentation (involving skin within radiation treatment field)
3) Reconstruction complications (defined as wound dehiscence, wound infection requiring the administration of oral or IV antibiotics, mastectomy skin flap necrosis, reconstructive flap necrosis not resulting in complete loss of flap, capsular contracture, or implant leakage/rupture/deflation.
4) Reconstruction failure (defined as loss of autologous reconstruction/flap, implant explantation, or unplanned expander removal without immediate replacement.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: [redacted]
All appropriate treatment areas should have access to a copy of the CTCAE.

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

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

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE ≤ 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

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

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

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

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

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

Hospitalization	• Grade 1 Timeframes	• Grade 2 Timeframes	• Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

9.3.2 Expedited AE reporting timelines defined

"24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.

"10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

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

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

Grade 3/4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.

Reporting of cases of secondary AML/MDS is to be done using the NCI/CTEP Secondary AML/MDS Report Form. New primary malignancies should be reported using study Form Notice of New Primary.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

Pregnancy loss is defined in CTCAE as "Death in utero." Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE version 5.0, the new malignancies (both second and secondary) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, (3) Treatment-related secondary malignancy, or (4) Neoplasms benign, malignant and unspecified-other. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and submitted, along with any additional medical information (form is available on the CTEP website at [redacted]). The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

10.0 DEVICE INFORMATION

10.1 Mepitel Film

Background: Mepitel Film is a transparent film dressing designed to protect fragile and sensitive skin and minimize the risk of skin breakdown. It can be used alone or in combination with other products.

Formulation: Mepitel Film with Safetac® technology is available in a variety of different sizes (6 x 7 cm, 10 x 12 cm, 10 x 25 cm, 15 x 20 cm). Only the 10 x 25 cm and 15 x 20 cm sizes will be used for this study.

Preparation and storage: Store as directed.

*Administration***:** Dry the skin/surrounding skin thoroughly. Remove the protection foil (printed Safetac®) to expose the adhesive. Position the dressing. Mepitel Film can be repositioned as long as the paper frame is intact. Remove the white paper frame. Do not stretch the dressing when applying. For best results, Mepitel Film shall overlap the dry surrounding skin by at least 5 cm for the larger sizes, in order to fixate securely. Firmly smooth out the dressing onto the skin. Mepitel Film can be removed without causing skin stripping and pain.

Procurement: Mepitel Film will be supplied in a kit and provided and shipped by the Mayo Clinic.

After receiving IRB approval for this study, each participating institution will order a supply of Mepitel Film from the Alliance by emailing the Alliance Mepitel Film Order Form to:

[redacted]

The A221803 Mepitel Film Kit Order Form can be found on the A221803 study page of the Alliance and CTSU websites. Site personnel should reorder additional Mepitel Film Kits based on their inventory levels, so that the Mayo Clinic staff may send additional supplies as needed. The initial supply should be sufficient to enroll additional patients at the site.

Within ninety days after the last patient is treated at the institution, any expired or remaining supplies should be destroyed according to institutional procedure.

Accountability

Sites should track receipt of the Mepital Film kits received from the Mayo Clinic and the quantity dispensed to patients. A Product Accountability Form can be found on the Alliance Website under A221803 *Supplemental Materials* or sites can choose to create their own form.

The Mepitel Film used in this study is subject to regulation by the FDA under an IDE application.

11.0 MEASUREMENT OF EFFECT

11.1 Patient reported Measures

11.1.1 mRISRAS (Appendix VI)

After consideration of the various assessment tools, we selected the mRISRAS for its strength in both the PRO and provider assessed domains when assessing radiation dermatitis (see Section 1.6). Given the psychometric properties of the RISRAS were evaluated in 1999, as part of this study we will conduct psychometric testing of the mRISRAS.[51]

The mRISRAS will be obtained at baseline (i.e. prior to the start of radiation), weekly during treatment, 7-14 days post treatment, and at the 3-month, 6-month, 1 year and 2-year follow-up visits. The PRO component of the mRISRAS will be evaluated for the primary endpoint, while the provider component and combined patient-provider scores will be evaluated as exploratory endpoints. The PRO section is feasible for the patient to complete in less than 5 minutes. Similarly, the provider scored component should take less than 5 minutes to complete. The mRISRAS is self-explanatory; however, when grading the erythema, the average erythema should be scored. More severe isolated areas of dermatitis will be accounted for with the additional domains, namely dry desquamation, moist desquamation, and necrosis.

11.1.2 PRO-CTCAE (See Appendix VIII)

To complement the primary endpoint, we will be collecting a short PRO-CTCAE questionnaire at baseline (i.e. prior to the start of radiation), weekly during treatment, 7-14 days post treatment, and at the 3-month, 6-month, 1 year and 2-year follow-ups. This questionnaire will include questions pertaining to radiation skin reaction, itching, general pain, and breast swelling and tenderness.

11.2 Site staff survey: Thin Film Clinical Utilization Survey (Appendix VIII)

This survey is not a validated metric but has been designed as a quick method for trained staff to track and record their experience in working with Mepitel Film (see Section 1.6). The survey tracks the frequency of film exchange, quantity of film used, incidence of film detachment, time and number of personnel required for exchange, and ease of use, allowing for descriptive reporting of these parameters. This survey should be completed once per week, prior to radiation therapy. It will take approximately 5 minutes to complete this survey. Recognizing that the application of Mepitel Film requires nursing/trained staff support, demonstration of its feasibility and ease of use will provide valuable data regarding its feasibility and generalizability. Furthermore, tracking the quantity of Mepitel Film used across patients will allow for an estimation of the average financial cost of this intervention.

11.3 Photographic assessment (Appendix III)

Baseline photographs will be obtained utilizing standardized views prior to the start of radiation, irrespective of the randomization arm. For patients randomized to the Mepitel Film arm, the photographs will be obtained prior to the application of Mepitel Film.

After completion of radiation, two additional sets of photographs will be obtained f**or patients randomized to the Mepitel Film Arm**; one prior to the removal of Mepitel Film, and the second at least one hour after the removal of the Mepitel Film. These latter photographs will be used for analysis of one of the pre-specified secondary endpoints: a centralized, blinded, provider assessment of the maximum severity of radiation dermatitis. **For patients randomized to the standard of care arm**, only one set of photographs will be obtained immediately following completion of radiation therapy. Photographs will also be obtained at the 7-14-day follow-up 3-month, 6 months, 1 year and 2-year follow-up visits for all patients. In addition to providing a blinded assessment, adding a centralized analysis also addresses potential institutional disparities inherent in a multi-center trial.

We recognize one limitation in evaluating photographs obtained in multiple institutions may be the quality and conformity of the photographs themselves. Standardized views (Appendix III) are provided to help mitigate these potential differences. The provider-scored mRISRAS was selected for this secondary endpoint, to provide uniformity and easier comparisons across endpoints. We felt that acquiring weekly blinded photographs would be both overly burdensome on the patient and provider and is further complicated by the fact that Mepitel Film would need to be removed prior to acquiring photographs and replaced after acquisition. As such, photographs will only be acquired before and after radiation therapy, as well as at the follow up visits at 7-14 days, 3 months, 6 months, 1 year and 2 years after radiation. This analysis will allow for an objective, blinded, centralized analysis of the maximal grade of radiation dermatitis, further strengthening the institutionally scored secondary endpoint.

Specifically, de-identified digital photographs obtained at baseline and following the completion of radiation (following removal of Mepitel for patients randomized to the Mepitel Film arm), will be viewed by a blinded panel of providers on a computer monitor. The degree of radiation dermatitis will be graded according to the mRISRAS (see Section 11.1.1, Section 13.4.2, and Section 13.5.2).

11.4 Psychometric Testing of mRISRAS

Comparative psychometric analysis of the mRISRAS will be carried out by procedures established by Huschka et al.[56] In brief, we will carry out simple correlational analyses followed by Bland-Altman procedures after translating the patient reported outcome measures onto a

common 0-100 scale.[57] We will also carry out a responsiveness analysis using the methods of Stockler and Guyatt.[58]

An expanded panel of providers assembled for the blinded assessment of radiation dermatitis, comprised of physicians and nurses (see Section 11.3) will also be provided with standardized images representing the various grades of radiation dermatitis. Providers will be asked to score the blinded images, at two different time points. We will use these assessments to evaluate both intra-rater reliability as well as inter-rater reliability. In addition to photos, the panel will also be provided with questions appropriate for validation, which will be used to analyze the face and content validity of the mRISRAS.

11.5 Criteria for Disease Response

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

11.5.1 Local Recurrence

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

11.5.2 Regional Recurrence

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

11.5.3 Distant Recurrence

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

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Protocol Treatment

Radiation therapy is to be given 5 days a week for 5-6 weeks. For patients randomized to Mepitel Film, the film will be applied prior to initiation of radiotherapy and will remain in place for up to 2 weeks following the completion of radiation. Please see the study calendar (Section 5.0) and the treatment section (Section 7.0) for treatment and follow-up time periods (Section 12.3).

12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

Intercurrent illness that prevents further administration of treatment

Unacceptable adverse event(s)

Patient decides to withdraw from the study

General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

Clinical progression

Patient non-compliance

Pregnancy

All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.

The product manufacturer can no longer provide the study agent.

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

12.3 Follow-up

12.3.1 Duration of Follow-up

Patients will undergo scheduled follow-up assessments at 7-14 days, 3 months, 6 months, 1 year and 2 years post radiation, then physical exams every 6 months until 5 years post radiation. See study calendar (Section 5.0).

12.3.2 Follow-up for Patients who Stop Study Treatment/Intervention Early

Follow up for patients who stop due to toxicity: For patients who are willing to continue to be followed per protocol, the same schedule of weekly management visits during treatment will be followed, as well as the same follow-up schedule. Additionally, all adverse events will be recorded, and patients will be asked to complete questionnaires, as specified in the protocol. An Off-Treatment form will be completed at the time of discontinuation of the intervention, which will record toxicities at the time of discontinuation, as well as the reason for discontinuation as specified by the patient.

For patients who withdraw from the study for any reason: For these patients, an Off-Treatment Form will be completed, which will record toxicities at the time of discontinuation, as well as the reason for discontinuation as specified by the patient.

Follow up for patients who receive non-protocol therapy: For patients who receive non-protocol therapy, the type of therapy received will be recorded as well as the dates, and the patients will continue to be followed per protocol. This includes all pre-specified management visits, follow-ups, data collection as outlined in the protocol, and questionnaires.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

Document the reason(s) for discontinuation of therapy on data forms.

Follow the patient for protocol endpoints as required by the Study Calendar.

12.5 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

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

Follow-up for ineligible patients who continue with protocol treatment

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

Follow-up for ineligible patients who discontinue protocol treatment

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

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

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

Baseline, off treatment, and post-treatment follow up (i.e., relapse, progression, and survival) data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a randomized, controlled clinical trial to determine the ability of Mepitel Film to reduce the severity of radiation dermatitis in patients undergoing post-mastectomy radiotherapy for breast cancer when compared with the existing institutional standard of care. Patients will be randomized in a 2:1 ratio to receive either Mepitel Film or the existing institutional standard of care. The 2:1 randomization favoring Mepitel Film was chosen to aid in recruitment given an expected enthusiasm for Mepitel Film based on previously published series. Randomization will be stratified on the basis of a breast reconstruction (yes; no), planned boost (yes; no), planned bolus (yes; no), and according to 3 levels of BMI, consistent with the established cut-offs as defined by the WHO (< 25; 25-29.99; and ≥ 30).[39]

13.2 Description of Randomization Routine

After a patient is registered they will be assigned to one of the two arms (Mepitel Film; existing institutional standard of care) in a 2:1 ratio utilizing a dynamic allocation algorithm based on the methods by Pocock and Simon.[63] The goal of the algorithm is to maintain arm balance with respect to the aforementioned stratification factors. In order to ensure that arm assignment is not deterministic, a level of randomness has been added to the algorithm such that patients will be assigned to the arm that leads to more imbalance 10% of the time. Dynamic allocation is a common approach in cancer clinical trials where we desire arms to be balanced across several prognostic factors. The method is considered robust because it ensures excellent arm balance overall and within the stratification factor levels, even with a large number of stratification factors [64]

13.3 Sample Size, Accrual Time, and Study Duration

Our statistical plan is informed by the largest single-institution, randomized, intra-patient-controlled study of Mepitel Film to date. This trial evaluated 78 patients receiving radiation therapy for breast cancer in which all patients had a portion of skin in the treatment field covered by Mepitel Film. Based on the combined patient- and provider-completed mRISRAS scores, utilization of Mepitel Film demonstrated a substantial 92% reduction in the extent of radiation-induced skin reactions, compared to an adjacent area of skin treated with aqueous cream.[42] The

findings translated into a large (> 0.80) effect size providing a benchmark used to guide our study's power analysis. The prophylactic effect was more marked, when based solely on the patient-completed mRISRAS scores. We expect the effect size will be attenuated given the multi-institutional nature of our study and due to the anticipated heterogeneity in the use of skin care products within our existing institutional standard of care arm, corresponding to a medium effect size of 0.5. An effect size of 0.5 is considered clinically relevant for our patient population receiving radiation therapy, and who are at risk for acute radiation dermatitis, which may compromise quality of life. Further, such an effect size has also been suggested to be clinically significant in general for patient-reported quality of life outcomes in cancer populations.[65]

Based on the aforementioned single-institution study, the distribution of the combined patient- and provider-completed mRISRAS scores (averaged over the post-randomization assessments) were positively skewed. As such, we propose using the AUC to summarize the sequence of repeated patient-completed mRISRAS scores for each patient. This summary measure tends to be approximately normally distributed. We hypothesize that the Mepitel Film arm will be associated with an improved AUC summary measure, corresponding to decreased patient-completed mRISRAS scores compared with institutional standard of care. With 192 patients randomized in a 2:1 ratio (128 Mepitel Film; 64 existing institutional standard of care), the study will have at least 90% power for a two-sample t-test to detect an effect size of -0.5 (Mepitel Film vs institutional standard of care) based on the AUC summary measure with a two-tailed alternative and a 5% Type I error rate. These results assume that two sequential tests are made using the O'Brien-Fleming spending function (see Section 13.4.3).

We anticipate that up to 10% of patients will not have met the eligibility criteria and/or not have submitted any mRISRAS data, and thus the target sample size will be inflated to 216 patients (144 Mepitel Film; 72 existing institutional standard of care). Importantly, any placement of the Mepitel Film will make the patient evaluable for the primary analysis provided that the patient had at least one patient-completed mRISRAS score, and was randomized (See Section 13.4.2 and the definition of the full analysis set).

Using conservative estimates, based on the Alliance Community Interest and Feasibility Survey conducted in May of 2018, we anticipate an accrual rate of 9 patients per month; therefore, to achieve the targeted accrual of 216 patients we anticipate that the accrual period will be approximately 24 months. Since the last protocol scheduled follow-up visit is 60 months post-radiation therapy, the corresponding total study duration will be approximately 84 months.

Because African American and Hispanic women may experience more significant acute toxicities we will make a concerted effort to accrue 25% (or 54 of 216) of the total patients in this combined category. Details on how we will achieve this important accrual goal are found in Section 13.9. Despite these efforts, if we still have not accrued 54 African American and Hispanic women once our study meets its planned accrual goal of 216 patients, we will close it to further accrual, with the exception of accruing the remaining Hispanic and African American women for a total of 54 such women. The justification for targeting a sample of 54 African American and Hispanic women and the analysis plan for this subpopulation is described in Section 13.9.

13.4 Statement for Primary Endpoint

13.4.1 Primary Endpoint

The primary endpoint is the serially measured patient-completed mRISRAS scores obtained at baseline (i.e. prior to the start of radiation), during weekly radiation therapy, at 10 (± 4) days post-radiation therapy, and at 3-months post-radiation therapy (Appendix VI). The primary endpoint was selected to assess the ability of Mepitel Film to impact

acute radiation dermatitis, which is defined as the skin toxicity secondary to radiation therapy that develops no later than 3 months post-radiation therapy. Moreover, the primary endpoint was chosen as a result of multiple discussions with the National Cancer Institute and National Cancer Institute reviewers. At a given time point, a patient-completed mRISRAS score ranges from 0 to 12, obtained from summing the 4 individual scores, where higher scores correspond to increased radiation-induced skin reactions. We anticipate that all patients will present with normal or near-normal skin based on the patient-completed mRISRAS score, corresponding to a baseline patient-completed mRISRAS score of < 4.

13.4.2 Analysis Plan for Primary Endpoint

The primary analysis will be based on the full analysis set, defined as all patients who were randomized and had at least one patient-completed mRISRAS score; furthermore, these patients will be analyzed in the arms to which they were randomized. Omitting patients from the primary analysis who do not provide any patient-completed mRISRAS data is not anticipated to cause any bias. The fact that patients do not provide any patient-completed mRISRAS data should be unrelated to the interventions to which patients were assigned. Furthermore, including a patient who does not provide any patient-completed mRISRAS data is not meaningful for analysis because the patient will not have a relevant contribution to the patient-reported outcome (PRO) estimate [66]. Nonetheless, any potential bias arising from the exclusion of randomized patients who do not provide any patient-completed mRISRAS data will be fully investigated (see Section 13.7)

In order to adjust for the stratification factors in the primary analysis, the AUC will be computed for the prophylactic arms based on estimated parameters from a repeated-measures (means) mixed model.[67] The outcome measures used in the repeated-measures (means) mixed model are the serially measured patient- completed mRISRAS scores obtained at baseline (i.e, prior to the start of radiation), weekly during radiation therapy, at 10 (± 4) days post-radiation therapy, and at 3-months post-radiation therapy. The covariates included in the model are indicator variables for all assessment time points, an indicator for the prophylactic method, the corresponding interaction terms, and the four stratification factors. This analytic approach, which is a likelihood method, to compare the prevention of radiation-induced dermatitis between the two prophylactic methods will preserve the full analysis set, allow for missing data (i.e. under the reasonable assumption of missing at random), and account for important covariates. Furthermore, it has been shown that this analytic approach is superior to a simple AUC summary measure in terms of both bias and precision.[67] Because of the gains in precision, the power analysis described in Section 13.3 is conservative; i.e. the power associated with the repeated-measures (means) mixed model will be greater since the addition of all available patient-completed mRISRAS scores will provide more information. We will report the summary statistic AUC for each arm, including the respective 95% confidence intervals, as well as the difference in AUC between the two arms along with the 95% confidence interval for the true, but unknown difference; the difference in AUC between arms will be estimated from the repeated-measures (means) mixed model and contrast for the summary statistic AUC. Further the two-sided *P*-value testing the null hypothesis of no difference (H_0: $\mu_{AUC_1} = \mu_{AUC_0}$) versus the two-sided alternative hypothesis that there is a difference (H_a: $\mu_{AUC_1} \neq \mu_{AUC_0}$) will be obtained from the repeated-measures (means) mixed model. Provided that the difference in AUC achieves statistical significance at the 5% level, the primary objective will have been met.

13.4.3 Interim and Final Analysis for Primary Endpoint

A single planned interim analysis of the primary endpoint for efficacy will be performed on the first 96 patients in the full analysis set who have completed the 3-month post-radiation therapy study procedures or withdrew from the study prior to completing the 3-month post-radiation therapy study procedures. The O'Brien-Fleming method will be used to control the Type I error rate and account for multiplicity and was chosen because it makes the early test at the interim analysis very conservative; the adjusted two-sided significance levels at the interim and final analysis are 0.003 and 0.049, respectively. The study may be suspended and terminated at the time of the interim analysis if the two-tailed p-value falls below 0.003. The final analysis of the primary endpoint will be performed on the first 192 assessable patients for efficacy. The interim and final analysis boundaries were generated using the PASS 15 power analysis and sample size software (2017).

13.4.4 Planned Sensitivity Analyses for Primary Endpoint

Recognizing that a number of additional variables may confound the interpretation of the results from the primary analysis, a sensitivity analysis is planned at the time of the final analysis to assess the robustness of the primary results in the presence of potential confounding variables such as reconstructed breast size, separation, and modality of boost. Further sensitivity analyses for the primary endpoint at the time of the final analysis will comprise subgroup analyses to ascertain whether the effect of Mepitel Film remains clinically robust according to various categories of topical products (e.g. aqueous creams, petroleum ointments, etc.) used on the existing institutional standard of care arm.

The study will be conducted at multiple sites. To account for within-site homogeneity in the primary endpoint, we will repeat the primary analysis and include a site-level random effect in the model.

Additionally, the primary analysis will be repeated on the per-protocol analysis set, defined as all patients in the full analysis set who were deemed eligible.

13.4.5 Planned Supplemental Analyses for Primary Endpoint

To further assess the robustness of the results obtained from the primary analysis, a supplemental analysis is planned. We will conduct longitudinal modeling of the patient-completed mRISRAS scores through 3-months post-radiation therapy. We anticipate that all patients will present with normal or near-normal skin based on the patient-completed mRISRAS score, corresponding to a baseline patient-completed mRISRAS score of < 4. The baseline patient-completed mRISRAS scores will be retained as part of the response vector. Furthermore, we will assume that the mean patient-completed mRISRAS scores in each arm are equal at baseline. Stated differently, the longitudinal model will include indicators for time (baseline being the reference level for time) and the interaction between arm and time, but no main effect of arm. The focus in this analysis will be on the interaction effect, which concerns arm comparisons of the patterns of changes in the mean patient-completed mRISRAS scores. In addition to plotting the model-based mean response profiles by arm, we will report each time-specific comparison between arms with a 95% confidence interval. Because arm assignment is random, constraining the randomization arm means at baseline to be equal will, in general, be more powerful than including the arm main effect and making no assumptions about arm differences in the mean response at baseline. Also this modeling approach for adjusting for baseline incorporates all available data at baseline, and at subsequent post-baseline time points in the analysis, despite the fact that some patients may be missing baseline patient-completed mRISRAS scores. This would not be the case if we analyzed the post-baseline patient-completed mRISRAS scores

and made no adjustment for the baseline patient-completed mRISRAS scores by including it as a covariate.

To further assess the robustness of the results obtained from the longitudinal model, the following covariates will be included: the four stratification factors, and reconstructed breast size, separation, and modality of boost. Unstructured covariance will initially be used, though alternative covariance structures (e.g. compound covariance) will be investigated with the final covariance structure selected based on minimization of the Akaike information criterion.

13.5 Statement for Secondary Endpoints

13.5.1 Secondary Endpoints

There are six secondary endpoints:

1. Centralized, blinded provider-completed mRISRAS scores obtained from a blinded grading of the photographs taken at the end of radiation therapy.
2. The serially measured non-blinded institutional provider-completed mRISRAS scores obtained at baseline (i.e. prior to the start of radiation), during weekly radiation therapy, at 10 (± 4) days post-radiation therapy, and at 3-months post-radiation therapy.
3. The serially measured combined patient- and provider-completed mRISRAS scores obtained at baseline (i.e. prior to the start of radiation), during weekly radiation therapy, at 10 (± 4) days post-radiation therapy, and at 3-months post-radiation therapy.
4. Time to biopsy proven local and/or regional failure.
5. Acute adverse events.
6. Chronic radiation therapy-related adverse events including skin and soft tissue fibrosis, telangiectasia, and hyperpigmentation.

13.5.2 Analysis Plan for Secondary Endpoints

The first three secondary endpoints defined in Section 13.5.1 may provide supportive information about the prophylactic effect of the Mepitel Film on the primary endpoint. Stated differently, the first three secondary endpoints characterize prophylactic effects related to the primary endpoint but may extend our understanding of that effect. The collection of these three secondary endpoints constitutes a family of secondary endpoints. A gatekeeping statistical strategy will be used to control the Type I error rate at 0.05 across the primary and this secondary family of endpoints such that when an effect on the primary endpoint is demonstrated, this family of secondary endpoints will be examined and may contribute important supportive information about the effectiveness of the Mepitel Film.

A fixed-sequence strategy will be applied to this family of three secondary endpoints defined above. Provided the study's primary objective is achieved, a between-arm comparison will be made in the centralized, blinded provider-completed mRISRAS scores obtained from a blinded grading of the photographs taken at the end of radiation therapy. Notably, a panel of radiation oncology providers will perform the blinded, central review to grade the photographs. Each provider will independently score each photograph, and the average score will be calculated for each patient. The provider-completed mRISRAS score ranges from 0 to 24, obtained from summing the 4 individual scores, where higher scores correspond to increased radiation-induced skin reactions. For this first secondary endpoint,

our hypothesis is that the Mepitel Film arm will be associated with lower centralized, blinded provider-completed mRISRAS scores. To ensure that the researchers scoring the photographs are blinded to the prophylactic method that was applied, the mRISRAS scores will be based on photographs following the removal of the Mepitel Film for patients randomized to the Mepitel Film arm. Based on the published single-institution study, the expectation is that the centralized, blinded provider-completed mRISRAS scores recorded at the end of radiation therapy will be positively skewed. Therefore, the Wilcoxon rank-sum test will be performed, and the methods of Hodges and Lehmann will be applied to compute a point estimate and confidence interval for the difference in medians between the two prophylactic methods. More specifically, patients will be ranked according to their centralized, blinded provider-completed mRISRAS scores recorded at the end of radiation therapy. The null hypothesis of no prophylactic effect is rejected, and the superiority of the Mepitel Film acknowledged, if in this ranking the 128 patients randomized to receive Mepitel Film rank sufficiently low. Under the null hypothesis (i.e. the distributions of both populations are equal), the probability that a centralized, blinded provider-completed mRISRAS score in the Mepitel Film arm is less than a centralized, blinded provider-completed mRISRAS score in the existing institutional standard of care arm is 0.5. Under the alternative hypothesis, we assume that this probability is 0.625. This probability corresponds to an effect size of 0.45 when the distribution is normal; based on the aforementioned largest single-institution study, the true but unknown effect size is likely to be considerably larger. With 192 patients (128 Mepitel Film; 64 existing institutional standard of care) and at a two-sided 5% significance level, the study will have at least 80% power to detect this shift in the population distributions, applying a two-sample Wilcoxon rank-sum test.

Provided that the first secondary endpoint achieves statistical significance at the 0.05 level, we will repeat the primary analysis defined in Section 13.4.2 based on the serially collected non-blinded institutional provider-completed mRISRAS scores. However, because a set of patients grouped within an institution are likely to respond similarly, we will also account for intra-institution correlation in the repeated-measures (means) mixed model with the inclusion of an institution random effect. Similarly, provided that the second secondary endpoint achieves statistical significance at the 0.05 level, we will repeat the above analysis based on the serially collected combined patient- and provider-completed mRISRAS scores. The combined patient- and provider-completed mRISRAS score ranges from 0 to 36, obtained from summing the patient-completed and the provider-completed mRISRAS scores, where higher scores correspond to increased radiation-induced skin reactions. Based on the aforementioned largest single institutional study, we anticipate a prophylactic effect size > 0.5 for each of these two secondary endpoints; therefore, both secondary endpoints are adequately powered given the stated sample size in Section 13.3.

Within this family of secondary endpoints, all three secondary endpoints are important clinically; however, the pre-specified testing order of the three secondary endpoints was determined by the likelihood of success.

Physical exam to evaluate local and/or regional recurrence will occur every 3 months for years 1, and then every 6 months for years 2-5. Based on the natural history of breast cancer, the rates of local and/or regional recurrence are expected to be low, or around 1-5% at 24 months based on a recent meta-analysis of individual patient data for 8,135 women in 22 randomized trials[68] furthermore, the estimated rates of local and/or regional recurrence are expected to be less than 10% by 60 months. To allow us to contextualize our study findings with those from this recent meta-analysis, another secondary endpoint is the time to biopsy proven local and/or regional failure, defined as the length of time from

the date of random assignment to the first instance of such an event; death will be treated as a competing event. A cumulative incidence function will be used to estimate the percentage of patients who experienced a local and/or regional failure within each arm at 6, 12, 24, 36, 48 and 60 months, treating death as a competing risk. Between-arm differences in the cumulative incidence functions will be tested for statistical significance using the procedure of Gray[69]. Furthermore, a cumulative incidence function regression model of Fine and Gray[70] will be used for multiple regression analyses; covariates included in the model will be the stratification factors and any potential confounding variables. Additionally, we will descriptively summarize the proportion of patients on each arm who experienced a locoregional recurrence by study month 60.

There are two other secondary endpoints that will be evaluated, and both are related to safety. The analysis of these safety endpoints will be based on the safety population, defined as all patients who initiated radiation; further the safety endpoints will be analyzed according to the intervention actually received. The constellation of acute and chronic adverse events (AEs) as scored using the National Cancer Institute Common Terminology Criteria for Adverse Events, v5.0 (CTCAE v5.0) will be summarized within arms by reporting the number and percentage of patients. Specifically, to evaluate the AE profiles associated with each arm, the maximum grade for each type of AE will be recorded for each patient and frequency tables will be reviewed to determine overall patterns. Additionally, the proportion of radiation dermatitis and skin and soft tissue fibrosis using NCI CTCAE v5.0 will be estimated within arms with the exact 95% confidence interval. Given the NCI CTCAE Version 5.0 scales for telangiectasia and hyperpigmentation are developed for total body surface area, they are not applicable to this study. As such, hyperpigmentation and telangiectasia will be evaluated on a 4-point scale, reflecting none, mild, moderate, and severe, and the corresponding number and percentage of patients reporting each will be presented according to arm. To evaluate the impact of chest wall separation on the constellation of AEs, we will display the AE profiles according to chest wall separation (> 25 cm; ≤ 25 cm) within each arm; additionally, other clinically meaningful separation thresholds will be explored depending on the distribution of the chest wall separation measurements.

13.5.3 Planned Sensitivity Analyses for Secondary Endpoints

As a supportive analysis for the first secondary endpoint (centralized, blinded provider-completed mRISRAS scores), the van Elteren statistic, which is an extension to the Wilcoxon rank-sum test that accounts for the stratification factors, will be calculated.

A sensitivity analysis is planned for the second and third secondary endpoints in order to assess the robustness of the results in the presence of potential confounding variables such as reconstructed breast size, separation, and modality of boost. Further sensitivity analyses for the second and third secondary endpoints will comprise subgroup analyses to ascertain whether the effect of Mepitel Film remains clinically robust according to various categories of topical products (e.g. aqueous creams, petroleum ointments, etc.) used on the existing institutional standard of care arm.

13.6 Statement for Exploratory Endpoints

13.6.1 Exploratory Endpoints

There are several exploratory endpoints that will be evaluated in an explorative fashion:

1. In patients who undergo breast reconstruction: Reconstruction complications within 24 months post-radiation therapy, defined as wound dehiscence, wound infection requiring the administration of oral or IV antibiotics, mastectomy skin

flap necrosis, reconstructive flap necrosis not resulting in complete loss of flap, capsular contracture, or implant leakage/rupture/deflation.

2. In patients who undergo breast reconstruction: Reconstruction failure within 24 months post-radiation therapy, defined as loss of autologous reconstruction/flap, implant explantation, or unplanned expander removal without immediate replacement.
3. Patient-reported itching, radiation skin reaction, pain, and breast swelling and tenderness as measured by the PRO-CTCAE.
4. The serially measured non-blinded patient- and provider-completed mRISRAS scores obtained at 6-months, 1-year, and 2-years post-radiation therapy.
5. In patients who receive the Mepitel Film: Serially collected response items from the Thin Film Clinical Utilization Survey.
6. Psychometric testing of the mRISRAS as outlined in Section 11.4.

13.6.2 Analysis Plan for Exploratory Endpoints

We anticipate that 30-50% of the 192 patients randomized will undergo breast reconstruction (a stratification factor at the time of randomization). Within this subset of patients, the estimated proportion of patients who experience reconstruction complications within 24 months post-radiation therapy will be reported according to arm along with the corresponding 95% confidence interval. Further, a between-arm comparison of the proportion of patients experiencing reconstruction complications within 24 months post-radiation therapy using the Fisher's exact test will be made. For this analysis, patients who terminate the study early and do not experience reconstruction complications prior to the time of early termination will conservatively be considered as having experienced reconstruction complications within the 24 months post-radiation therapy; it is expected that the number of patients terminating the study early will be low and balanced across arms. In a similar fashion, a between-arm comparison of the proportion of patients experiencing reconstruction failure within 24 months post-radiation therapy using the Fisher's exact test will be made.

As a supplemental analysis within the subset of patients who undergo breast reconstruction, a cumulative incidence function will be applied to the time to first reconstruction complication, defined as the length of time from the date of random assignment to the first reconstruction complication. Death and disease recurrence will be treated as competing events. Specifically, a cumulative incidence function will be used to estimate the percentage of patients who experienced a reconstruction complication within each arm, treating death and disease recurrence as competing risks. Between-arm differences in the cumulative incidence functions will be tested for statistical significance using the procedure of Gray[69]. Furthermore, a cumulative incidence function regression model of Fine and Gray [70] will be used for multiple regression analyses; covariates included in the model will be the stratification factors and any potential confounding variables. The supplemental analyses described herein will also be applied to time to reconstruction failure.

To determine the frequency and severity of patient-reported itching, radiation skin reaction, pain, and breast swelling and tenderness, as measured by the PRO-CTCAE, the maximum grade for each of these events will be recorded for each patient and frequency tables will be generated. The descriptive analysis of the PRO-CTCAE endpoints will be based on the

safety population, defined as all patients who initiated radiation; further the safety endpoints will be analyzed according to the intervention actually received.

To determine the long-term severity of radiation dermatitis, the serially measured combined patient- and provider-completed mRISRAS scores obtained at 6-months, 1-year, and 2-years post-radiation therapy, will be descriptively summarized within each arm. These analyses are intended to complement and further contextualize the analyses related to chronic skin toxicity.

Lastly, descriptive summaries of the response items captured by the Thin Film Clinical Utilization Survey (Appendix VIII) will be tabulated for the patients who receive the Mepitel Film.

13.7 Missing Data

Baseline patient/disease characteristics will be evaluated between randomized patients who do not provide any patient-completed mRISRAS data with randomized patients who do provide at least one patient-completed mRISRAS score and therefore part of the full analysis set. As described in Section 13.4.2, the primary analysis uses a likelihood method to compare the prevention of radiation-induced dermatitis between the two prophylactic methods and, therefore, allows for missing mRISRAS scores under the reasonable assumption of missing at random. It is anticipated that partially completed mRISRAS questions completed by the patient will be infrequent. In the event that a patient completes ≤ 2 of the 4 individual mRISRAS questions, the corresponding patient-completed mRISRAS score will remain missing; however, if a patient completes 3 of the 4 individual questions (i.e. more than half of the questions), then the patient-completed mRISRAS score will be the average of the 3 scores multiplied by 4. The amount of missing data in Alliance clinical trials, especially with respect to PROs, have been minimized, typically less than 5%, due to a long history of targeted approaches[71]. In the event that the proportion of missing patient information is larger than 5%, we will examine the missingness mechanism by modeling indicators of missing values as a function of baseline patient characteristics, observed outcomes, and missingness of outcomes. Based on this diagnostic exercise, we will determine whether we can enhance the analyses by incorporating certain covariates or whether we need to explore more advanced methods. As sensitivity analyses, however, we will apply a recently developed macro which uses 20 different imputation approaches to missing data that was developed by the Alliance Statistics and Data Center. This approach involves the production of imputed datasets that are subsequently re-analyzed alongside the initial data, and compare the results across the spectrum of approaches to assess the veracity of the initial findings.[72,73]

13.8 Study Monitoring

13.8.1 Data and Safety Monitoring Board

This study will be monitored by the Alliance Data and Safety Monitoring Board (DSMB), an NCI-approved functioning body, twice per year. The DSMB follows the Alliance Policies and Procedures for all randomized phase III trials. The DSMB will review administrative information, accrual, including accrual of African American and Hispanic women, adverse events, and interim analysis results. All summary findings of the DSMB will be communicated to study investigators by the Alliance.

13.8.2 Data Mapping Utility (DMU)

This study has been assigned Demography monitoring.

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

Note: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

13.8.3 Adverse Event Stopping Rule

Throughout the course of the study, we will monitor AEs in both study arms, and may suspend accrual if patients are experiencing a large number of AEs.

Accrual will be temporarily suspended to this study if 3 or more of the first 27 patients experience any grade 3+ AEs, excluding radiation dermatitis, that the study team considers to be at least possibly related to Mepitel film (i.e. an AE with attribute specified as "possible", "probable", or "definite"), and the toxicity is higher in the Mepitel film arm (on a percentage basis). In addition, accrual will be temporarily suspended to this study if 3 or more of the first 27 patients experience grade 3+ radiation dermatitis and the percentage of patients is higher in the Mepitel film arm.

The AE stopping rule may be modified if during the course of the study, new information becomes available which suggests that such a modification is necessary, or if, after temporarily stopping accrual, the above rule is found to be overly conservative.

PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting. PRO-CTCAE data are included for exploratory purposes and not currently intended for use in data safety monitoring or adverse event stopping rules.

13.8.4 Accrual Monitoring Stopping Rule

Patient accrual will be closely monitored by the investigators and study statistician on a bi-weekly basis. If the accrual rate falls below 50% of expected accrual rate, investigators will carefully review feedback from sites and consider taking measures to encourage patient enrollment, updating our accrual plan in Section 1.7 as needed.

13.9 Inclusion of Women and Minorities

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

As African American women have been shown to demonstrate higher rates of moist desquamation, they would be expected to gain a substantial benefit from Mepitel Film.[4,38,40] Furthermore, as poor and Hispanic women have been shown to be more likely to receive a chest wall boost, this places them at high risk of more severe skin reactions.[41] As such, we will make a concerted effort to accrue 25% (or 54 of 216) of the total patients in this combined category. For that, we have a Health Disparities Committee Co-Chair on this protocol, to ensure a focused effort at achieving this important accrual goal of African American and Hispanic women. Furthermore, we will enlist NCI Community Oncology Research Program (NCORP) Principal Investigators who specialize in minority and underserved patient populations and we will activate the study at NCORP sites enriched in African American and Hispanic women receiving treatment for breast cancer.

Once our study meets its planned accrual goal, we will close it to further accrual, with the exception of accruing Hispanic and African American patients, with the plan of obtaining 25% (or 54) of the 216 total patients in this combined category. We have also included the stratification factor planned boost (yes; no) at the time of randomization to ensure balance across the arms. Within the 54 Hispanic and African American study population (due to randomization approximately 36 on Mepitel Film and 18 on institutional standard of care), we will estimate the proportion of acute grade 3+ radiation dermatitis, and skin and soft tissue fibrosis using NCI CTCAE v5.0 within each arm along with the corresponding two-sided 90% confidence interval. Assuming that the proportion of such events on the Mepitel Film arm is 10% and the proportion on the institutional standard of care arm is as low 45%, the lower bound of the two-sided 90%

confidence interval for the difference in proportions constitutes a clinically important difference (90% CI: 0.14, 0.56); furthermore, sample sizes of 18 and 36 produce a two-sided 90% confidence interval for the difference in population proportions with a width that is at most 0.42, i.e. assuming that the proportion of grade 3+ acute toxicity is 10% in the Mepitel Film arm and ranges from 45% to 70% in the institutional standard of care arm.

As part of our analysis plan, we will descriptively evaluate racial/ethnic and socioeconomic differences in our results. The area deprivation index (ADI), which is an existing measure of neighborhood socioeconomic disadvantage, is calculated based on an individual zip code+4 and will be used as a proxy for socioeconomic status; zip code+4 level ADI for the United States is publicly available. Although the study is not prospectively powered to detect interaction effects between arm and either race/ethnicity or socioeconomic status, we will explore through planned subgroup analyses whether the magnitude of the Mepitel Film effect, as measured by skin reaction severity and incidence of moist desquamation, differs in a clinically meaningful way across race/ethnicity categories or by socioeconomic status; skin reaction severity is measured by the patient- and provider-completed mRISRAS scores over time and moist desquamation is a component of the provider-completed mRISRAS (score > 0 on 0 [Normal skin] to 4 [Deep or red purple] point scale).

We are not aware of any evidence suggesting differential effects in other subsets defined by race or ethnicity. Expected sizes of race by ethnicity subsets for patients randomized to this study are shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	2	0	0	0	2
Asian	5	0	0	0	5
Native Hawaiian or Other Pacific Islander	2	0	0	0	2
Black or African American	35	0	0	0	35
White	144	2	19	0	165
More Than One Race	7	0	0	0	7
Total	195	2	19	0	216

14.0 CORRELATIVE AND COMPANION STUDIES

There will be one substudy and all patients are encouraged to participate.

14.1 Correlative Science (Alliance A221803-ST1)

14.1.1 Background

Radiation induced acute toxicities have been correlated with alterations of the microbiome in cancer treatment. In patients undergoing radiation to the abdomen or pelvis, alterations in the gut microbiome were found to correlate with the development of diarrhea.[74] Observed changes in the microbiome include relative population differences in species as well as a decrease in overall microbial diversity.[75] Changes in microbial diversity have also been documented in the oral microbiome during radiotherapy for head and neck cancer.[76] The microbiome has also been linked to chemotherapy induced toxicities.[77] Recent work completed at Mayo Clinic demonstrated that the microbiomes found in the breast parenchyma of non-cancer patients and breast cancer patients are distinct, raising the question of whether the background microbiome plays a role in carcinogenesis itself.[78]

To date, the relationship of the skin microbiome to the development of radiation dermatitis is unknown. Radiation dermatitis is an inflammatory skin reaction. The relationship between the epithelial barrier, immune defense, and cutaneous microbiome has emerged as a key system for maintaining balance in the development of other inflammatory skin conditions.[61] Alterations in the skin microbiome appear to play a role in the development and exacerbation of inflammatory skin conditions such as eczema and atopic dermatitis. In these conditions, severity of disease has been linked with increased colonization by *Staphylococcus aureus* (*S. aureus*).[79,80] Recently, commensal bacteria normally present on human skin were found to play a central role in controlling *S. aureu*s through the release of antimicrobial peptides. Additionally, these commensal bacteria were found to be significantly reduced in atopic dermatitis.[81] Dilute sodium hypochlorite baths are effective at decreasing levels of pathogenic bacteria, and have demonstrated efficacy in reducing the severity of atopic dermatitis.[82-85] In addition, in pre-clinical mouse models, the use of topical hypochlorite (bleach) prior to radiation decreased the severity of acute radiation dermatitis and prevented skin ulceration.[86] Interestingly, case studies have found *S. aureus* to be a contributor to severe radiation dermatitis as well.[87] Taken together, these data suggest that further study of the microbiome during acute radiation dermatitis may improve mechanistic understanding and identify future key therapeutic strategies.

This correlative study is designed to evaluate the changes that occur in the microbiome secondary to ionizing radiation alone as well as the ability of Mepitel Film to stabilize the skin microbiome and/or prevent superinfection, as we hypothesize. Given the vast number of cancer patients who experience radiation dermatitis, improvement in our understanding would be meaningful and encourage development of future novel interventions, with the potential to alleviate one of the most common radiation associated morbidities.

14.2.2 Objectives

a) To determine the impact of ionizing radiation on the skin microbiome, including quantitative analysis of *S. aureus*.

b) To determine the effect of Mepitel Film on the skin microbiome, including quantitative analysis of *S. aureus*.

c) To determine the impact of Mepitel Film on radiation-induced changes in the skin microbiome, including quantitative analysis of *S. aureus*.

d) To correlate the aforementioned alterations in the skin microbiome with the observed severity of radiation dermatitis.

14.2.3 Methods

Skin swabs will be obtained from all patients who provide consent to participate in the optional study, prior to the start of radiation, irrespective of the randomization arm (see Section 6.2.2, Appendix X). For patients randomized to the Mepitel Film arm, the aforementioned baseline swabs and photographs will be obtained prior to the application of Mepitel Film. A second set of skin swabs will also be obtained following the final fraction of radiation. For patients randomized to the Mepitel Film arm, the final swabs will be obtained immediately following removal of the Mepitel Film. All swabs will be frozen as outlined in Section 6.2.1.

Following completion of study accrual and collection of the final skin swabs, specimens will be transferred from the Alliance Biorepository at Mayo Clinic (Mayo BAP) to the University of Minnesota Genomics Center, where the 16S microbiome, and droplet digital PCR (ddPCR) analyses will be conducted. Work overseen by:

[redacted]

DNA extraction and dual indexing 16S PCR

Following extraction of the DNA, a two-step PCR protocol will then be used to amplify the V3-V5 region of the 16S rRNA gene.[88] Dual indexing will be conducted per Gohl et al, 2016. Briefly PCR products will be quantified, normalized, pooled, and concentrated at approximately 1 µg of material to 10 µl. The pooled sample will then be size-selected, cleaned, and eluted for quantification.

Sequencing

Pooled sample will be denatured with NaOH, diluted, and heat denatured prior to sequencing.

Droplet Digital PCR (ddPCR)

Quantitative analysis of *S. aureus* will be conducted using ddPCR

Pipeline for processing of 16S data

Microbiome and ddPCR data generated at the University of Minnesota Genomics Center will be securely transferred to the Division of Biomedical Statistics & Informatics, Section of Computational Genomics, at Mayo Clinic at Rochester, MN for analysis by Alliance Faculty. These raw data will be analyzed using bioinformatics to analyze the beta-diversity, taxonomy, and phylogeny.

15.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING

Sites are encouraged to accrue minority patients on the trial.

The site needs to provide information or proposed accrual plan to support that they can accrue 5-10 patients on this trial over 6 months.

15.1 Site Approval Form

Institutions that are interested in participating in this study must meet the following requirements:

The site must have the ability to accept durable medical equipment according to their institutional procedures and state or local requirements. States that do **NOT** allow us to provide durable medical equipment are: **Alabama, Colorado, Georgia, Hawaii, Indiana, Mississippi, Nevada, New Jersey, North Carolina, Oregon, and Tennessee.**

In order for the Alliance to monitor starter supply distribution, institutions are asked to document their commitment to the requirements of the study on the Site Approval Form. The "Site Approval form" must be downloaded from the "Supplemental materials" tab of the Alliance and CTSU websites. The form must be completed and submitted to the following email address: [redacted]

The signed and approved Site Approval form must then be submitted to the CTSU regulatory portal as indicated in Section 4.2.4 to begin patient enrollment.

15.2 Mepital Film Online Training Video

Sites must have sufficient staff to re-apply Mepitel Film on average, weekly during treatment. It can be applied by either one or two people, and step-by-step instructions are included in Section 7.2. In addition, a short training video on proper application and removal will be available and should be sufficient to train healthcare providers who are unfamiliar with its use. The training video will be posted on CLASS, and sites are required to view the video. We will also provide training sessions at the twice-yearly Alliance meetings and the study team will be available to address questions, as needed. There will be no formal credentialing required on this trial with respect to this training.

At each participating site, a research nurse or clinical research professional (CRP) (person who intends to apply Mepitel film on the patient) will receive training on the mepitel film application using the online video training module through the Compliance, Learning, and SOP Solutions (CLASS) website, hyperlink below.

[redacted]

By going to the web address above, staff will be brought to the CTEP-IAM Single Sign On page, where they must enter their CTEP-IAM account username and password. After logging into CLASS, staff will be brought directly to the Alliance A221803 Mepitel Film application training. To gain access to the course and begin training, click the Enroll button associated with the course.

Once the first site member has completed their training, CLASS will automatically communicate with the Regulatory Support System (RSS) and the protocol-specific training requirement will be complied. Assuming all other regulatory requirements have been satisfied, the site will receive site registration approval.

Any questions or concerns regarding accessing the training module in CLASS may be directed to the CLASS Help Desk at [redacted]

Any further questions or concerns regarding Mepitel film applications may be addressed to the study chairs.

15.3 IROC Institutional Credentialing

Either 3D conformal or Intensity Modulated Radiation Therapy (IMRT) planning techniques are allowed on this study.

15.3.1 IROC Institutional Requirements

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

Web link for credentialing procedures and instructions: [redacted]

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

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17.0 MODEL INFORMED CONSENT

Research Study Informed Consent Document

Study Title for Participants: Testing the application of Mepitel Film during radiation therapy to reduce radiation related redness and peeling in breast cancer patients following mastectomy

Official Study Title for Internet Search on [redacted]: Alliance A221803: "Mepitel Film for the Reduction of Radiation Dermatitis in Breast Cancer Patients Undergoing Post-Mastectomy Radiation Therapy: A Randomized Phase III Clinical Trial" **(NCT04989504)**

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have been diagnosed with breast cancer and your doctor has recommended that you receive radiation therapy after your mastectomy to reduce the risk of your breast cancer coming back. Radiation therapy can cause side effects such as redness and peeling of the area of radiation.

Taking part in this study is your choice.

You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

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

Why is this study being done?

This study is being done to answer the following question:

Can we reduce the severity of skin redness and peeling in the area of radiation by applying Mepitel Film during radiation therapy as compared to your usual care?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for reducing skin redness and peeling in the area of radiation. The usual approach is defined as care most people get for skin redness and peeling in the area of radiation.

What is the usual approach to my skin redness and peeling in the area of radiation?

The usual approach for patients who are not in a study is to use aqueous creams, petroleum ointments, aloe vera, acetic acid soaks or prescription medications such as mometasone or lidocaine. This approach varies depending on which hospital you are receiving your treatment.

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will either have Mepitel Film applied on your breast or chest wall at least once every 2 weeks before your radiation therapy for up to six weeks, or you will get your usual care for up to six weeks during radiation therapy. You will also complete a questionnaire about your symptoms before you start your radiation treatment, every week during your radiation treatment, and at your 7 to 14 day, 3-month, 6-month, 1-year and 2-year follow-up visits after you complete your radiation treatment.

Photographs of both your breasts or chest wall will also be captured before and at the end of your radiation treatment, as well as at your 7 to 14 day, 3-month, 6-month, 1-year, and 2-year follow up visits.

After you finish your radiation treatment, your doctor will continue to follow your condition for five years after you complete your radiation treatment and watch you for side effects. These follow up visits will include a physical (including height, weight and collection of your medical history) and will occur 7 to 14 days after your treatment, and at 3 months, 6 months, 9 months, 1 year and then every 6 months until 5 years after you complete your radiation treatment. After 2 years, your follow up visit may be performed by your local doctor.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the study approach may not be as good as your usual approach at reducing the severity of your skin redness and peeling in the area of radiation.

There is also a risk that you could have side effects from the study approach. These side effects may be worse and may be different than you would get with the usual approach for your skin redness and peeling in the area of radiation.

Some of the most common side effects that the study doctors know about are:

- Itching
- Rash

There may be some risks that the study doctors do not yet know about.

Benefits

There is evidence that Mepitel Film is effective in reducing the severity of skin redness and peeling in the area of radiation. It is not possible to know now if Mepitel Film will reduce the severity of redness and peeling on the area of radiation as compared to the usual approach. This study will help the study doctors learn things that will help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

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

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.

- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- You become pregnant while on the study.
- The study is stopped by the Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (NCI). The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

You will be getting radiation therapy after mastectomy to treat your breast cancer. This treatment may cause skin redness and peeling in the area of radiation. The purpose of this study is to test if applying Mepitel Film before you get radiation reduces the severity of your symptoms. Mepitel Film is a thin flexible film applied to the skin. It is designed to cover sensitive skin and is approved by the FDA for use in wound care. Mepitel has not specifically been approved by the FDA for use in radiation, however, it has been approved for use in this trial. Mepitel Film will be compared to the usual skin treatment during five to six weeks of your radiation treatment. The addition of Mepitel Film could reduce the skin redness and peeling; however, it could also cause side effects, which are described in the risks section below.

There will be about 216 people taking part in this study.

This study will help the study doctors find out if this different approach is better than the usual approach. To decide if it is better, the study doctors will be looking to see if the study approach reduces the severity of redness and peeling in the area of radiation compared to the usual approach.

What are the study groups?

This study has 2 study groups. You will be informed which group you are in. Both groups receive radiation for five to six weeks as recommended by their doctor.

- **Group 1**

  If you are in this group, you will receive radiation treatment five days a week for five to six weeks as recommended by your doctor. Your skin reaction will be managed by your doctor with their usual recommendations.

  Photographs of both your breasts or chest wall will also be captured before and at the end of your radiation treatment, as well as at your 7 to 14 day, 3-month, 6-month, 1-year, and 2-year follow up visits, and sent to the Alliance database so that an assessment of side effects can be made. Each set of photos includes 6 standard front and side facing views.

A member of your care team or designated medical photographer will take the photos. Your face will not be captured on these photographs and they will not include your name or other personal information.

There will be about 72 people in this group.

- **Group 2**

  If you are in this group, you will receive radiation treatment for five to six weeks as recommended by your doctor. Before radiation treatment is started, you will have a dressing called Mepitel Film applied to your breast or chest wall before your radiation treatment every week.

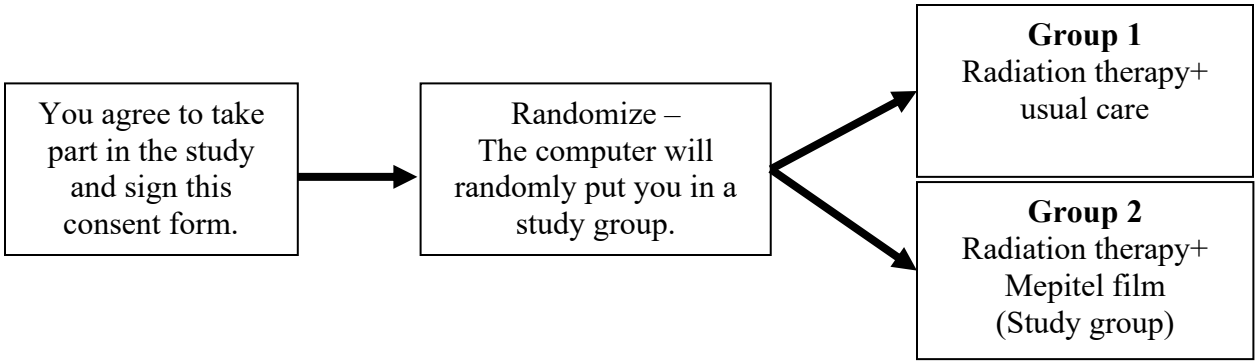
  Your study nurse will apply this film before your scheduled radiation treatment at your clinic visits. You can expect approximately 15 to 20 minutes for film placement or replacement. When the film is replaced or removed, it is gently peeled off in approximately 1 to 3 minutes. You can shower with the film in place. You should not soak in a tub or scrub at the film. You will be given instructions to contact your doctor if the film is peeling or not adhering. Peeling film may require a nursing visit for replacement prior to the weekly appointment.

  Photographs of both your breasts or chest wall will also be captured before and the end of your radiation treatment. At the end of radiation treatment, one set of photographs will be captured before removal of the Mepitel Film, and one set after the removal of Mepitel Film, and sent to the Alliance database so that an assessment of side effects can be made. Photographs of both your breasts or chest wall will be also be captured at your 7 to 14 day, 3-month, 6-month, 1-year, and 2-year follow up visits. Each set of photos includes 6 standard front and side facing views. A member of your care team or designated medical photographer will take the photos. Your face will not be captured on these photographs and they will not include your name or other personal information.

  There will be about 144 people in this group.

We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose, and you cannot choose which study group you are in. You will be put into a group by chance. You will have twice the chance of being in Group 2 than in Group 1.

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



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

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study.

If you are an English speaker and choose to take part in this study, you will be asked to fill out forms with questions about your physical and emotional well-being. Researchers will use this information to learn more about how cancer treatment affects people.

Since these forms are being used for research, the responses you provide will not be shared with your study doctor. If you have any serious health issues or other concerns, please talk with your doctor or nurse right away.
You will be asked to fill out these forms in person at the following times:

- Before you start your radiation treatment
- Weekly while receiving radiation (5-6 weeks)
- 7 to 14-day follow-up
- 3-month follow-up
- 6-month follow-up
- 1-year follow-up
- 2-year follow-up

Each form will take about 10 minutes to complete. The forms will ask about things like skin symptoms such as itchiness, tenderness, pulling. You don't have to answer any question that makes you feel uncomfortable.

In addition, after you finish your radiation treatment, your doctor will continue to follow your condition for five years after you complete your radiation treatment and watch you for side effects. These follow up visits will include a physical (including height, weight and the collection of your medical history) and will occur at 3 months, 6 months, 9 months, 1 year and then every 6 months until 5 years after you complete your radiation treatment. After 2 years, your follow up visit may be performed by your local doctor.

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

General Risks

If you choose to take part in this study, there is a risk that the Mepitel Film may not be as good as the usual approach for reducing skin redness and peeling. Mepitel Film does not reduce the dose of radiation at the skin. Since it may reduce side effects of skin redness, one possible but unlikely risk is that it might reduce the effect of the radiation at cancer cells in the skin surface and lead to a higher chance of the cancer returning.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The radiation that all patients will be receiving could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use while receiving radiation treatment.

Side Effect Risks

All patients on this study receive radiation therapy. The study intervention is Mepitel Film for those who are assigned to Group 2. Side effects listed in the following sections about radiation therapy are possible for any woman undergoing radiation and are not specific to this trial. The radiation therapy used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood.

There is also a risk that you could have other side effects from the radiation therapy.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.

Device Risks

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

Possible Side Effects of Mepitel Film (applies only if you are assigned to Group 2)

COMMON, SOME MAY BE SERIOUS In 100 people on whom Mepitel Film is applied, more than 20 and up to 100 may have:
• Mild discomfort during removal

OCCASIONAL, SOME MAY BE SERIOUS In 100 people on whom Mepitel Film is applied, from 4 to 20 may have:
• Skin rash • Itching • Pulling sensation

Possible Side Effects of Radiation Therapy (applies to both groups- this is part of the usual approach for treating this type of cancer)

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

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

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

Apart from the above risks, you may also have permanent skin darkening in the area receiving radiation.

What are my responsibilities in this study?

If you choose to take part in this study, you will need to:

- Keep your study appointments.
- Tell your doctor about:
  - all medications and supplements you are taking
  - any side effects
  - any doctors' visits or hospital stays outside of this study
  - if you have been or are currently in another research study.

For women: Do not get pregnant or breastfeed while you are receiving radiation treatment. **For men:** Do not father a baby while you are receiving radiation treatment. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety and prevent and treat side effects.
- your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. For this study, you or your insurance provider will not have to pay for the Mepitel Film or the cost of applying the film while you take part in this study.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.
- Need to take more time off work.
- Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

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

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Your face will not be captured on the photographs of your breasts taken for the study. These photographs will not include your name or other personal information and will be saved in the Alliance database.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor, Alliance for Clinical trials in Oncology.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.

- The NCI and the groups it works with to review research including the Imaging and Radiation Oncology Core (IROC).

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

Where can I get more information?

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

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

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

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

Optional studies that you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading this optional study hope the results will help other people with your condition in the future. The results will not be added to your medical records and you or your study doctor will not know the results.

Taking part in this optional study is your choice. You can still take part in the main study even if you say "no" to this study. There is no penalty for saying "no." You and your insurance company will not be billed for this optional study. If you sign up for, but cannot complete this study for any reason, you can still take part in the main study.

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

Optional sample collections for known laboratory studies and/or storage for possible future studies

Researchers are trying to learn more about cancer and other health problems using samples such as skin swabs from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Known future studies

If you choose to take part in this optional study, researchers will collect skin swabs for research on how bacterial populations normally present on your skin may change during radiation, or as a result of Mepitel Film. You will need to have skin swabs for the study, collected before you start your radiation treatment, and after your radiation treatment is finished. This will involve rubbing a moistened swab on your breast, or chest wall skin in eight different areas. These samples will be analyzed using laboratory techniques to identify the types and populations if different bacteria present on your skin at the times the swabs were collected.

Unknown future studies

If you choose to take part in this optional study, skin swabs will be collected and stored. Storing samples for future studies is called "biobanking." The biobank is being run by the Alliance Biorepository at Mayo Clinic and is supported by the NCI. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request identifies who they are and what their planned research project is. Before getting the samples and data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you.

Right now, we don't know what research may be done in the future using your skin swab samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your samples.

What is involved in this optional sample collection?

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

1. Skin swab samples will be collected before you start your radiation treatment, and after your radiation treatment is finished. This will involve rubbing a moistened swab on your breast, or chest wall skin in eight different areas.
2. Your sample will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
3. Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
4. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- The most common risks related to collecting skin swabs from your breast are mild discomfort, like rubbing Q- tips on the skin.
- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: [redacted]

How will information about me be kept private?

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

1. They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.
2. Researchers who study your sample and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

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

Are there any costs or payments to this optional sample collection?

There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

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

What if I have questions about this optional sample collection?

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

Please circle your answer below to show if you would or would not like to take part in each optional study:

Samples for known future studies:

I agree that my samples and related health information may be used for the laboratory study described above.

YES NO

Samples for unknown future studies:

I agree that my samples and related health information may be kept in a biobank for use in future health research.

YES NO

Contact for Future Research

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Participant's signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature

APPENDIX I PREVIOUS STUDY ABSTRACT

Initial experience with barrier film dressing for dermatitis prophylaxis in breast proton therapy.

K. Corbin[1], K. Roberts[1], S. James[1], S. Park[1], E. Yan[1], K. Klein[1], J. Lubahn[1], C. Loprinzi[1], I. Petersen[1], R. Mutter[1].
[1]Mayo Clinic, Radiation Oncology, Rochester, USA.

Purpose/Background: Radiation dermatitis is a common acute toxicity of breast cancer radiotherapy. Mepitel Film (MF) appears to reduce acute radiation dermatitis (RD) in photon patients. We report the feasibility and initial outcomes of PMRT patients treated with proton beam (PBT) and MF.

Methods: Patients were treated with multifield optimized pencil-beam scanning IMPT to the chest wall and regional lymph nodes, most commonly with a 2-field oblique beam arrangement, per institutional standards. The median prescription dose was 50 Gy (RBE 1.1) in 25. Skin dose was individualized, with typical planning goals of D90>90% and D1cc < 105%. MF was applied prior to treatment and replaced approximately weekly. Common toxicity criteria for adverse effects (CTCAE v 5.0) patient-reported outcomes (PRO) version of the CTCAE (PRO-CTCAE) and 10-point linear analog scales (LASA) were collected prospectively to evaluate skin toxicity.

Results: 33 patients underwent proton PMRT with MF. Twenty were reconstructed with tissue expanders and 13 were non-reconstructed. Four of 33 discontinued, for pruritis (2), film non-adherence (1), and unrelated rash (1). Median D1cc skin of 103.5% (Range: 95.8-120%). Physician assessed, and patient reported outcomes are shown in Table 1. Maximal physician reported RD was grade 1-2 in 97% at completion. Of 9 that described severe or very severe radiation burns, 8 were judged as having Grade 1-2 RD.

Conclusions: Post mastectomy IMPT with MF was feasible, resulting in promising patient and physician reported acute toxicity. Based on this preliminary experience, we are planning a randomized trial of MF in PMRT.

Physician-Assessed AEs	**CTCAE Grade**	**Baseline (n=33)**	**Post-RT (n=33)**
Physician Reported Radiation Dermatitis	1	0%	64%
	2	0%	33%
	3	0%	3%
Patient-Reported Outcomes	**LASA$^{\alpha, \beta}$**	**Baseline (n=28)**	**Post-RT (n=29)**
Quality of Life $^{\alpha}$	7-10	76%	74%
	4-6	24%	22%
	0-3	0%	4%
Flaking or Peeling$^{\beta}$	0-3	100%	86%
	4-6	0	7%
	7-10	0	7%

Bleeding or fluid leaking[β]	0-3	100%	93%
	4-6	0	0%
	7-10	0	7%
Itching [β]	0-3	100%	52%
	4-6	0	24%
	7-10	0	24%
Radiation Skin Burns[‡]	None	100%	21%
	Mild	0%	34%
	moderate	0%	14%
	Severe	0%	21%
	Very severe	0%	10%

LASA[α]: Reported on a scale of 1-10 (0 indicating "as bad as it can be" and 10 indicating "as good as it can be")

LASA[β]: Reported on a scale of 1-10 (0 indicating "none" and 10 indicating "as bad as it can be")

CTCAE-PRO[‡]: Reported on a 5-point scale (none, mild, moderate, severe, very severe)

APPENDIX II FIGURES 1 AND 2 SHOWING MEPITEL FILM EFFECT ON RADIATION DERMATITIS

Figure 1. Mepitel Film was applied to the medial portion of the treatment field prior to the initiation of therapy and was re-applied weekly. Images of two representative patients (A, B) were taken on the final day of radiotherapy and show a marked reduction in severity of dermatitis in the Mepitel covered areas compared to the internal control.

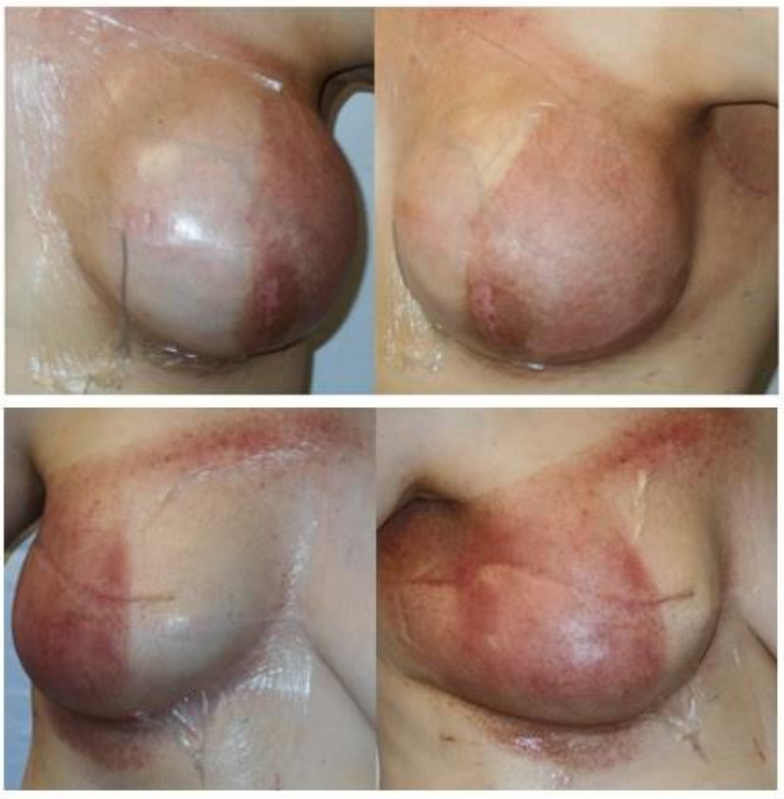
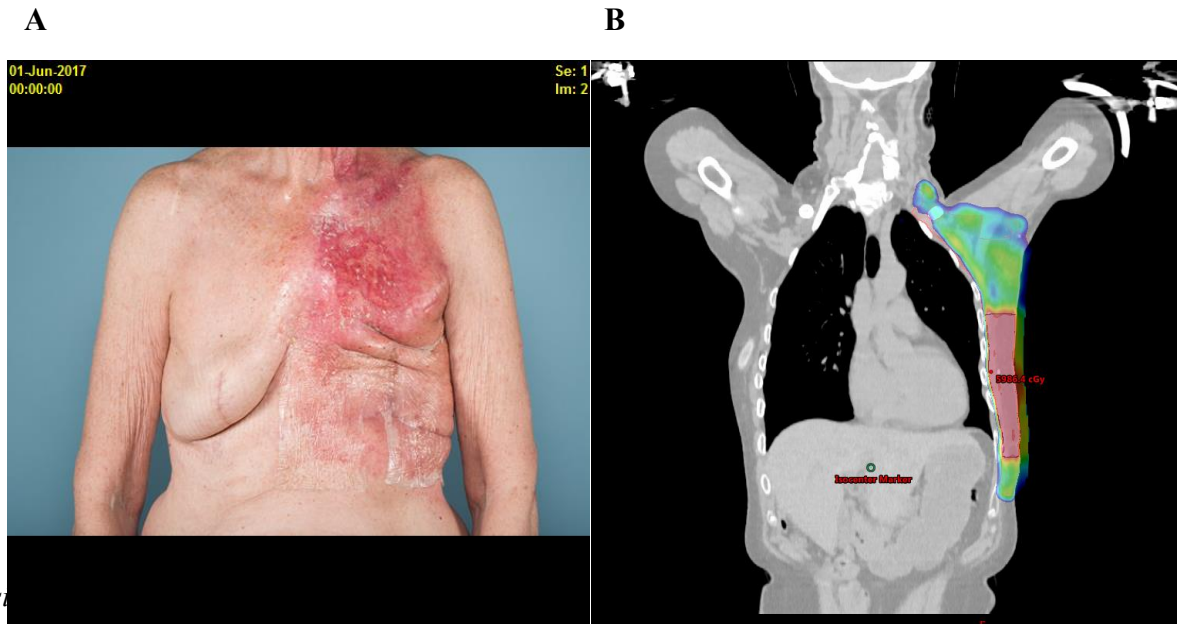
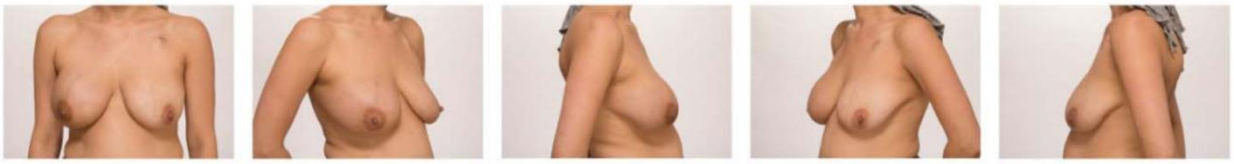


Figure 2. Radiation dermatitis in a post-mastectomy patient treated with spot scanning intensity modulated proton therapy. Mepitel Film covers the inferior half of the chest wall where a higher boost dose of radiotherapy was administered. Despite the higher dose, the Mepitel covered area demonstrates decreased radiation dermatitis (A). Dose color wash demonstrates the area of higher radiation dose in red (B).



APPENDIX III PHOTOGRAPHY STANDARD BREAST PROTOCOL

Standard Breast Protocol - Arms at side for first view



APPENDIX IV SKIN CARE FORM

Please record all skin care products patient is currently applying to treatment area (circle all that apply)

a. Aqueous cream (i.e. Vanicream, Eucerin, etc.)

b. Petroleum based ointments (Aquaphor, Vaseline, etc.)

c. Aloe Vera

d. Vinegar soaks

e. Prescription creams/ointments (i.e. mometasone, lidocaine, topical antibiotics)

f. Wound care products (i.e xeroform gauze, silvadene, etc.)

APPENDIX V NON-CTCAE TOXICITIES

Please complete at baseline prior to radiation therapy, weekly while on treatment, and at the 7-14 day, 3-month, 6-months, 1 year and 2-year post treatment follow up visits.

1) Provider assessment of Hyperpigmentation and Telangiectasia. Circle appropriate grade.

(Grade: 1 = none, 2 = mild, 3 = moderate, 4 = severe).

Hyperpigmentation:	1	2	3	4
Telangiectasia	1	2	3	4

2) Provider assessment of reconstruction complications

Did the patient experience a reconstruction complication, defined as wound dehiscence, wound infection requiring the administration of oral or IV antibiotics, mastectomy skin flap necrosis, reconstructive flap necrosis not resulting in complete loss of flap, capsular contracture, or implant leakage/rupture/deflation? Circle appropriate response.

Yes / No

If yes, specify type of complication _____

Date of complication _____

3) Provider assessment of reconstruction failure.

Did the patient experience a reconstruction failure, defined as loss of autologous reconstruction/flap, implant explantation, or unplanned expander removal without immediate replacement? Circle appropriate response.

Yes / No

If yes, specify type of failure_____

Date of failure _____

APPENDIX VI mRISRAS- MODIFIED RADIATION INDUCED REACTION ASSESSMENT SCALE [26,50]

*****FOR HEALTHCARE PROFESSIONAL USE ONLY*****

INSTRUCTIONS FOR USE

1) Assess the patient at least once a week, recording the date and no. of fractions received.

2) Rate "Erythema" by recording the degree of color change.

3) Rate "Dry desquamation", "Moist desquamation", and "Necrosis" by evaluating the proportion (%) of the treatment area affected by that particular reaction.

Healthcare Professional Scale

Erythema (E)	0 (Normal skin)	1 (Dusky pink)	2 (Dull red)	3 (Brilliant red)	4 (Deep red-purple)
Dry desquamation (DD)	0 (Normal Skin)	1 (<25%)	2 (≥25-50%)	3 (>50-75%)	4 (>75-100%)
Moist desquamation (MD)	0 (Normal Skin)	1.5 (<25%)	3.0 (≥25-50%)	4.5 (>50-75%)	6.0 (>75-100%)
Necrosis (N)	0 (Normal Skin)	2.5 (<25%)	5 (≥25-50%)	7.5 (>50-75%)	10 (>75-100%)

Note: See next page for patient completed portion.

INSTRUCTIONS: Please fill out the patient symptoms scale by selecting the option that best describes your condition for the given question.

Patient Symptoms Scale

Symptoms	NOT AT ALL	A LITTLE	QUITE A BIT	VERY MUCH
Do you have any tenderness, discomfort or pain of your skin in the treatment area?	**0**	**1**	**2**	**3**
Does your skin in the treatment area itch?	**0**	**1**	**2**	**3**
Do you have a burning sensation of your skin in the treatment area?	**0**	**1**	**2**	**3**
To what extent has your skin reaction and your symptoms affected your day to day activities?	**0**	**1**	**2**	**3**

APPENDIX VII NCI PRO-CTCAE ITEM ™ ENGLISH

Item Library version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days.

PRO-CTCAE™ Symptom Term: Radiation skin reaction						
1.	In the last 7 days, what was the SEVERITY of your SKIN BURNS FROM RADIATION at their WORST?					
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe	○ Not applicable

PRO-CTCAE™ Symptom Term: Itching					
2.	In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

PRO-CTCAE™ Symptom Term: General pain					
3.	In the last 7 days, how OFTEN did you have PAIN?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	Almost constant
	In the last 7 days, what was the SEVERITY of your PAIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN INTERFERE with your usual or daily				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

PRO-CTCAE™ Symptom Term: Breast swelling and tenderness					
4.	In the last 7 days, what was the SEVERITY of your BREAST AREA ENLARGEMENT OR TENDERNESS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

APPENDIX VIII THIN FILM CLINICAL UTILIZATION SURVEY

(To be completed by Site Staff who apply and remove Mepitel Film)

Patient Clinic #_____

Date_____

Please answer the following questions regarding the ***Mepitel Film dressing?*** This survey applies to the treatment side only.

- Describe the Changes to the dressing this week?
  Entire Partial No change of film dressing (skip the rest of the items)

- If this was a partial dressing change, what percent of the dressings were changed?
  20% 40% 60% 80%

- How many pieces of Mepitel Film were over the last week?

Size	**Quantity used**
10 x 12 cm	_____
10 x 25 cm	_____
15 x 20 cm	_____

- Was the film patched or changed over the last week? How many times was patching/changing required?

- How many personnel were required for dressing change?

- What is the estimated number of minutes spend with film dressing changes over the last week?

- Please rate the ease of application
  1 2 3 4 5 6 7 8 9 10
  (Easy) (Difficult)

APPENDIX IX SKIN CARE GUIDELINES FOR PATIENT

Recommended guidelines apply ONLY to the area without Mepitel Film.

1. Patient may follow their normal skin care and bathing habits. Recommended skin care products are outlined below.

2. Aqueous cream: Recommended for maintaining moisture of skin.
    a. Moisturizer should be applied twice a day to all areas being treated.
    b. Vanicream is the recommended moisturizer unless the patient has a known allergy.

3. Petroleum based ointments: Recommended for patients as they develop visible erythema.
    a. Aquaphor is the recommended ointment.
    b. Ointment should be applied twice a day and include all areas being treated.

4. Prescription medications: Recommended for local discomfort, burning, or itching.
    a. Mometasone 0.1%, applied to the affected area daily for pruritis.
    b. Topical Lidocaine may be used for local burning or discomfort.

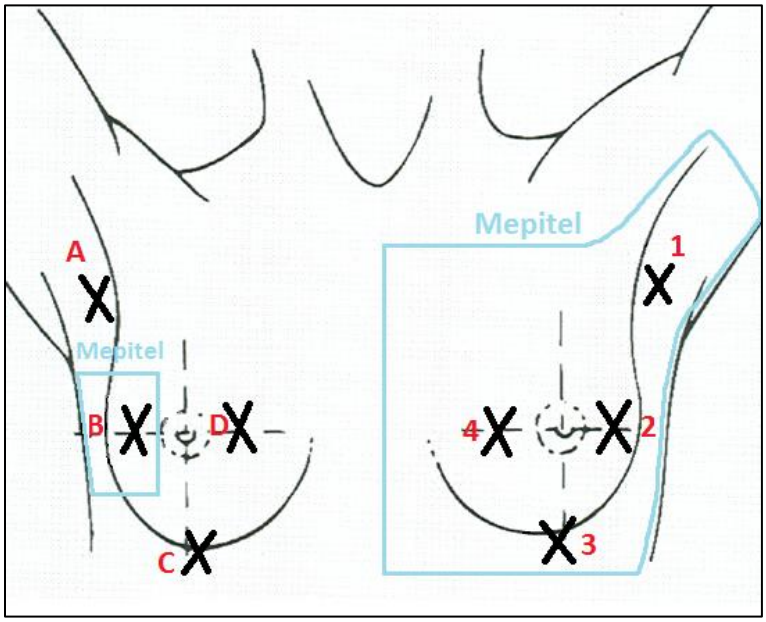
5. Wound care: Recommended interventions for moist skin reaction.
    a. Replace aqueous creams with Aquaphor.
    b. Acetic acid soaks
    c. Silvadene cream, applied to affected area unless the patient has a known allergy.
    d. Xeroform dressing, applied to affected area.

6. If allergies or other negative reactions, contact a member of the study team or your treating physician.

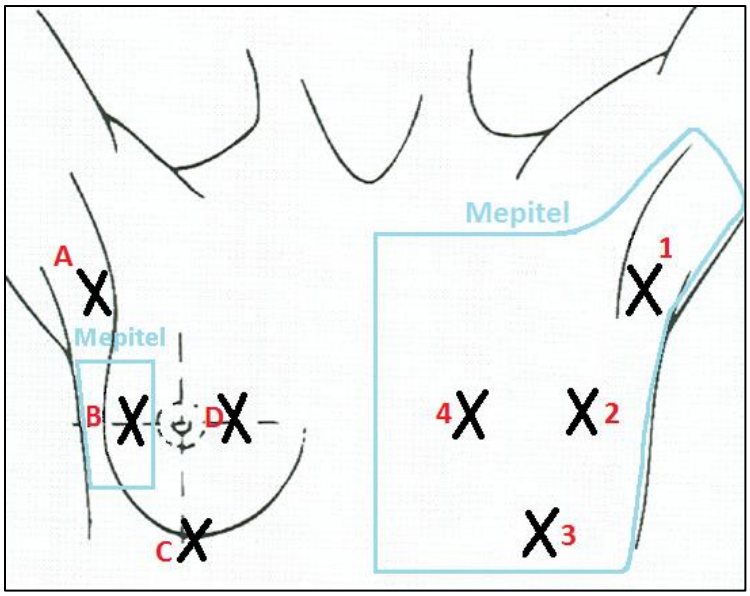
APPENDIX X SKIN SWAB SAMPLE COLLECTION INSTRUCTIONS

<u>Swab collection # 1</u> (START), LEFT SIDED TREATMENT

With Reconstruction



No Reconstruction



<u>Location:</u> Please collect 8 swabs from the areas outlined by the 'X' on the adjacent diagram. There will be two collection times during the study, with eight swabs being collected at each collection time.

<u>Collection 2 (Start):</u> 8 samples collected <u>before</u> Mepitel Film is placed, <u>before</u> radiation starts.

Pre-label tubes as follows, with 'S' referring to 'Start.'

S-A, S-B, S-C, S-D / S-1, S-2, S-3, S-4

Swabs obtained from the patient's RIGHT side should always be marked A, B, C, D as follows:

A – Right axilla
B – Right Lateral breast mound/chestwall
C – Right Inframammary fold or corresponding area on the chestwall for non-reconstructed patients.
D – Right medial breast mound/chestwall

Swabs obtained from a patient's LEFT side should always be marked 1, 2, 3, 4 as follows:

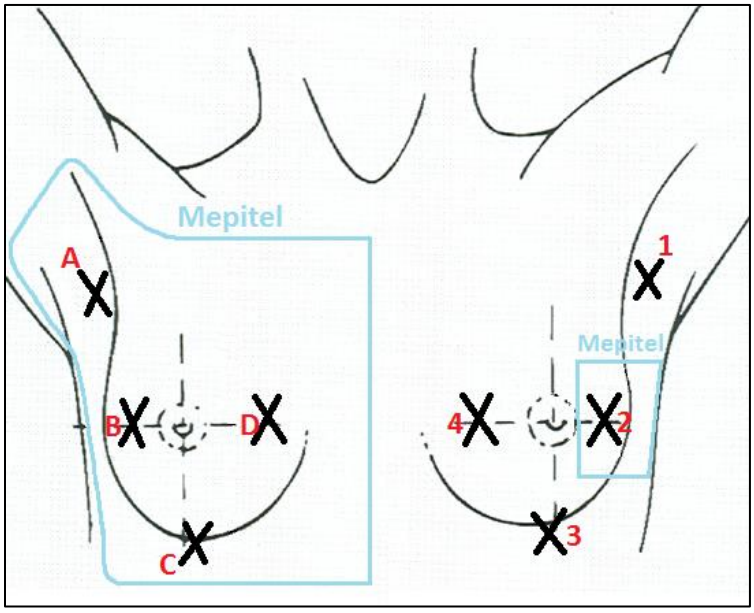
1 – Left axilla
2 – Left Lateral breast mound/chestwall
3 – Left Inframammary fold or corresponding area on the chestwall for non-reconstructed patients.
4 – Left medial breast mound/chestwall

The labeling should be identical regardless of whether the patient is receiving right or left sided treatment.

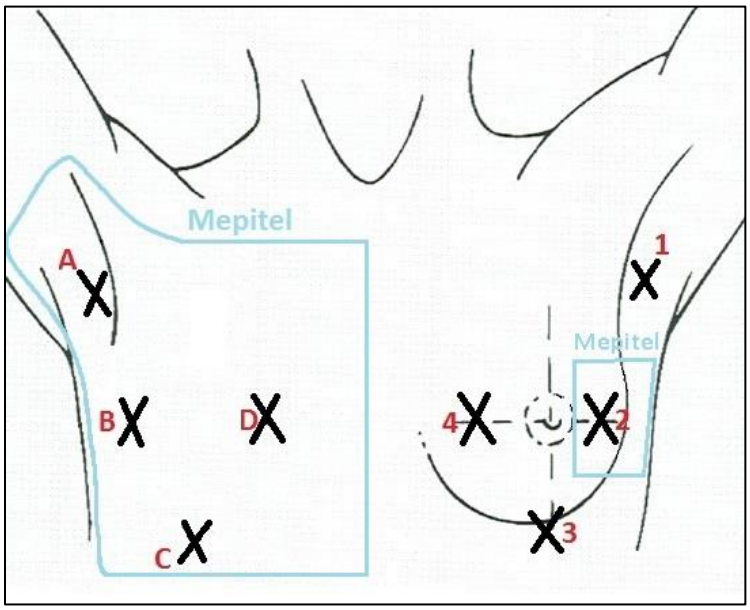
Mepitel Film will not yet be applied, so you will have to plan accordingly and ensure the area you are swabbing will be covered by Mepitel Film if intended.

<u>Swab collection # 1</u> (START), RIGHT SIDED TREATMENT

With Reconstruction



No Reconstruction



<u>Location:</u> Please collect 8 swabs from the areas outlined by the 'X' on the adjacent diagram. There will be two collection times during the study, with eight swabs being collected at each collection time.

<u>Collection 1 (Start):</u> 8 samples collected <u>before</u> Mepitel Film is placed, and <u>before</u> radiation starts.

Pre-label tubes as follows, with 'S' referring to 'Start.'

S-A, S-B, S-C, S-D / S-1, S-2, S-3, S-4

Swabs obtained from the patient's RIGHT side should always be marked A, B, C, D as follows:

A – Right axilla
B – Right Lateral breast mound/chestwall
C – Right Inframammary fold or corresponding area on the chestwall for non-reconstructed patients.
D – Right medial breast mound/chestwall

Swabs obtained from a patient's LEFT side should always be marked 1, 2, 3, 4 as follows:

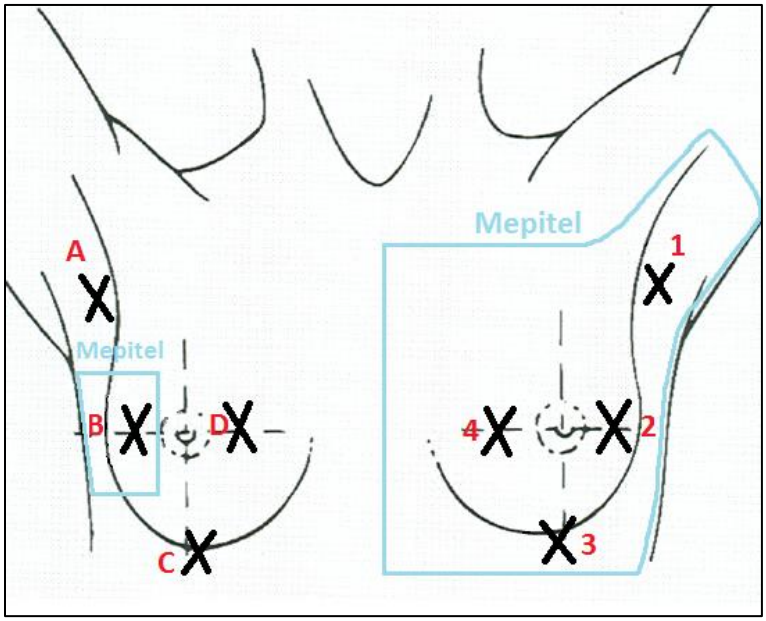
1 – Left axilla
2 – Left Lateral breast mound/chestwall
3 – Left Inframammary fold or corresponding area on the chestwall for non-reconstructed patients.
4 – Left medial breast mound/chestwall

The labeling should be identical regardless of whether the patient is receiving right or left sided treatment.

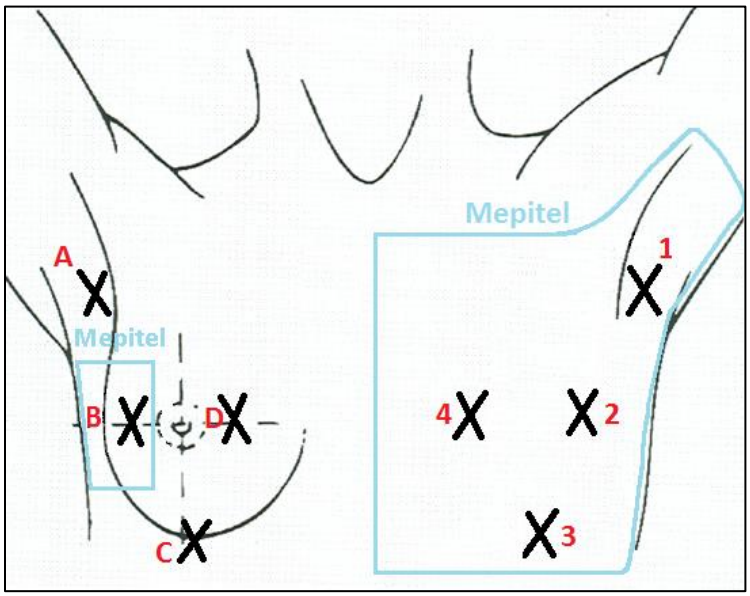
Mepitel Film will not yet be applied, so you will have to plan accordingly and ensure the area you are swabbing will be covered by Mepitel Film if intended.

<u>Swab collection # 2</u> (FINAL), LEFT SIDED TREATMENT

With Reconstruction



No Reconstruction



<u>Location:</u> Please collect 8 swabs from the areas outlined by the 'X' on the adjacent diagram. There will be two collection times during the study, with eight swabs being collected at each collection time.

<u>Collection 2 (Final):</u> 8 samples collected <u>after</u> Mepitel is removed, <u>following</u> final radiation.

Pre-label tubes as follows, with 'F' referring to 'Final.'

F-A, F-B, F-C, F-D / F-1, F-2, F-3, F-4

Swabs obtained from the patient's RIGHT side should always be marked A, B, C, D as follows:

A – Right axilla
B – Right Lateral breast mound/chestwall
C – Right Inframammary fold or corresponding area on the chestwall for non-reconstructed patients.
D – Right medial breast mound/chestwall

Swabs obtained from a patient's LEFT side should always be marked 1, 2, 3, 4 as follows:

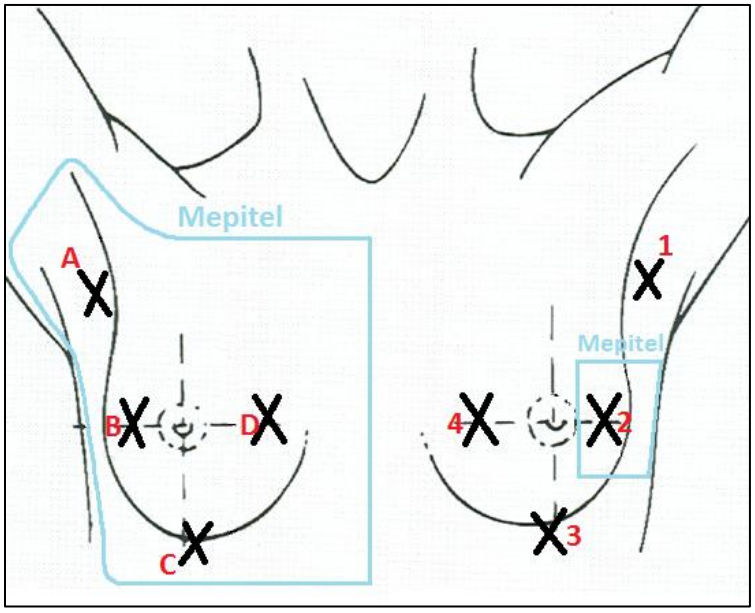
1 – Left axilla
2 – Left Lateral breast mound/chestwall
3 – Left Inframammary fold or corresponding area on the chestwall for non-reconstructed patients.
4 – Left medial breast mound/chestwall

The labeling should be identical regardless of whether the patient is receiving right or left sided treatment.

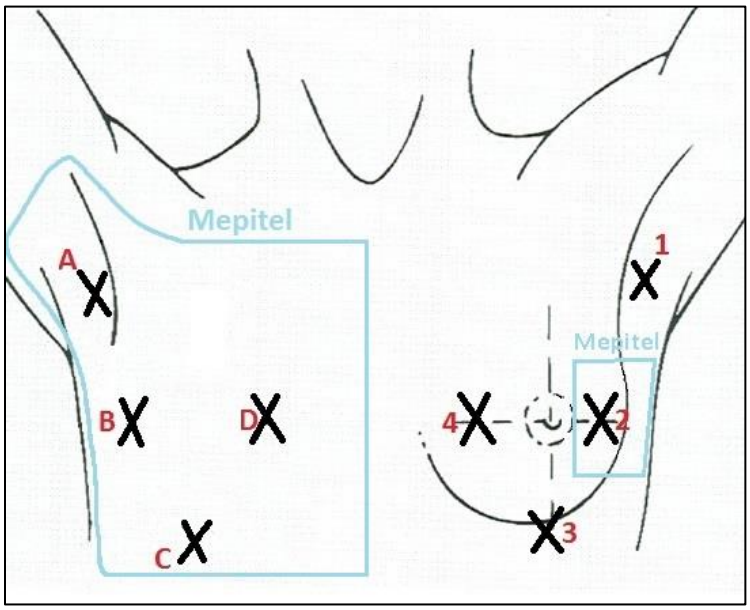
Mepitel Film will be removed prior to final swab collection, so you will have to plan accordingly and ensure the area you are swabbing was covered by Mepitel Film if intended.

<u>Swab collection # 2</u> (FINAL), RIGHT SIDED TREATMENT

With Reconstruction



No Reconstruction



<u>Location:</u> Please collect 8 swabs from the areas outlined by the 'X' on the adjacent diagram. There will be two collection times during the study, with eight swabs being collected at each collection time.

<u>Collection 2 (Final):</u> 8 samples collected <u>after</u> Mepitel is removed, <u>following</u> final radiation.

Pre-label tubes as follows, with 'F' referring to 'Final.'

F-A, F-B, F-C, F-D / F-1, F-2, F-3, F-4

Swabs obtained from the patient's RIGHT side should always be marked A, B, C, D as follows:

A – Right axilla
B – Right Lateral breast mound/chestwall
C – Right Inframammary fold or corresponding area on the chestwall for non-reconstructed patients.
D – Right medial breast mound/chestwall

Swabs obtained from a patient's LEFT side should always be marked 1, 2, 3, 4 as follows:

1 – Left axilla
2 – Left Lateral breast mound/chestwall
3 – Left Inframammary fold or corresponding area on the chestwall for non-reconstructed patients.
4 – Left medial breast mound/chestwall

The labeling should be identical regardless of whether the patient is receiving right or left sided treatment.

Mepitel Film will be removed prior to final swab collection, so you will have to plan accordingly and ensure the area you are swabbing was covered by Mepitel Film if intended.

APPENDIX XI DIMINISHED SKIN REACTION OBSERVED WITH THE USE OF MEPITEL FILM

Measurements conducted using a single 10x10 anterior 6X beam with Gafchromic film and Markus parallel plate ion chamber and normalized at each depth to the dose at Dmax.

Depth (mm)	% Increase with Mepitel Film
0.19	3%
0.54	2%
0.93	1%
1.02	2%
1.3	2%
1.56	1%
1.67	0%

APPENDIX XII PATIENT INFORMATION SHEETS

Patient Completed Booklet A
(Baseline)

You have been given a booklet to complete for this study. This booklet contains some questions about your 'quality-of-life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You are being asked to complete a questionnaire booklet for this study. This booklet must be completed before you begin your radiation treatment. It contains the following questionnaires:

    - mRISRAS
    - PRO-CTCAE questionnaire

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

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

4. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

5. After completing this booklet, please return it to your nurse or physician.

Thank you for taking the time to help us.

Patient Completed Booklet B
(Weekly and end of radiation treatment)

You have been given a booklet to complete for this study. This booklet contains some questions about your 'quality-of-life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You are being asked to complete a questionnaire booklet for this study. This booklet must be completed every week, before you begin your radiation treatment and at the end of your treatment. It contains the following questionnaires:

    - mRISRAS
    - PRO-CTCAE questionnaire

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

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

4. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

5. After completing this booklet, please return it to your nurse or physician.

Thank you for taking the time to help us.

Patient Completed Booklet C
(Follow up at 7-14 days, 3 months, 6 months, 1 year and 2 years after radiation treatment)

You have been given a booklet to complete for this study. This booklet contains some questions about your 'quality-of-life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You are being asked to complete a questionnaire booklet for this study. This booklet must be completed at the following clinic visits: 7-14 days, 3 months, 6 months, 1 year and 2 years after radiation treatment. It contains the following questionnaires:

    - mRISRAS
    - PRO-CTCAE questionnaire

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

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

4. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

5. After completing this booklet, please return it to your nurse or physician.

Thank you for taking the time to help us.