An unblinded, open-label study evaluating the safety of Silverlon® to manage radiation dermatitis

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PROTOCOL APPROVAL

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1. PURPOSE, BACKGROUND, AND OBJECTIVES

1.1. PURPOSE

This is a safety study of a commercially available silver-nylon burn dressing (Silverlon® Dressing, Argentum Medical, Geneva, IL) in a cohort of patients likely to develop radiation dermatitis from undergoing radiation therapy as a treatment for breast cancer. The goal is to establish the safety of the use of Silverlon® as a topical dressing to manage radiation dermatitis. While the results are expected to be applicable to any cancer site requiring radiation therapy, we will select patients with breast cancer as a group most easily studied for radiation dermatitis.

1.2 BACKGROUND AND RATIONALE

Of the 1.6 million patients newly diagnosed with cancer annually in the United States, approximately 50% will receive radiation therapy at some point in their treatment. Up to 95% of these patients will experience adverse skin reactions, collectively termed radiation dermatitis. (1, 2, 3, 4, 5, 6, 7). Up to 60% of patients with breast radiation will develop Radiation Therapy Oncology Group (RTOG) Late Radiation Morbidity Scoring grade 2 or 3 toxicity and 30-40% of unselected patients will develop moist desquamation (8). Because of the almost universal occurrence of radiation dermatitis in patients undergoing radiation therapy, there is great interest in finding skin care products that can prevent or ameliorate this injury while providing an optimal environment to assure safe and effective tissue repair.

Currently, there are no effective products that prevent radiation dermatitis; therefore, emphasis has shifted to treatment of visible signs of sustained radiation-induced skin reaction. Unfortunately, no standard treatment recommendations exist for the prevention of radiation skin toxicity (9). There is 'significant heterogeneity in clinical practice' (10), a 'relative lack of high-quality evidence to support specific management strategies' (10), and no product is universally successful or recognized as best. There are hundreds of products used to treat radiation dermatitis, nearly all being employed 'off-label'. There are approximately 20 products with US Food and Drug Administration (FDA) pre-marketing clearance for the indication of radiation dermatitis. Most are passive protective hydrogel emulsions or dressings. All have been approved through the 'substantial equivalence' 510(k) pathway, without clinical trials in radiation dermatitis prior to approval.

Silver-nylon dressings (Silverlon® Wound/Burn Contact Dressings, Argentum Medical, Geneva IL) are comprised of a single layer of knitted nylon fiber substrate coated with metallic silver. Commercially marketed since 2003, Silverlon® dressings have 16 FDA 510(k) premarketing clearances, with both over-the-counter and prescription indications. Silverlon® dressings have also been the standard US military dressings for burns and traumatic injuries for over 15 years (11) and are the standard of care for transatlantic aeromedical evacuation of burn patients (12,13). Silverlon® Dressings are indicated for use up to 7 days for partial and full thickness wounds including traumatic wounds, surgical wounds (donor and graft sites, incisions), first and second degree thermal burns, as well as dermal ulcers (stage I-IV pressure sores, venous stasis ulcers, arterial ulcers, diabetic ulcers), vascular access or peripheral IV sites, orthopedic external pin sites and wound drain sites. Additionally, Silverlon® Dressings are indicated for the management of infected wounds, as the silver in the dressing provides an antimicrobial barrier that may be helpful in managing these wounds. Silverlon® Dressings are a non-adherent wound contact layer that reduces pain during dressing changes and evaporation of moisture in the dressing may soothe the wound. (14)

Several clinical studies performed in Canada have demonstrated the utility of silver-nylon dressings in the management of radiation dermatitis. Vuong et al (15) performed a Phase II study of 15 patients with anal or gynecologic cancers who received radiation therapy of 45-54 Gy in 25-30 fractions with concurrent chemotherapy. In this population, the expected incidence of radiation dermatitis is 100% with 43-78% of patients progressing to severe (RTOG grade 3-4) radiation dermatitis (15). Silver-nylon dressings were placed starting on day 1 of radiation therapy and maintained continuously until 2 weeks after conclusion of the radiation therapy. Dressings were removed during radiation application and for bathing. A control group received silver sulfadiazine starting at the occurrence of symptomatic dermatitis. The mean RTOG radiation dermatitis severity score was 1.15 (SD= 0.4) for silver nylon group compared to 2.62 (SD 0.48) in the control group ($p < 0.0001$).

A follow-up Phase III study by Niazi et al (16) had similar results. Forty-two anal or rectal cancer patients undergoing high-dose radiation therapy of 50 to 60 Gy in 28-33 fractions with concurrent chemotherapy were randomized to silver-nylon or silver sulfadiazine treatment. Silver-nylon dressings were placed on day 1 of therapy and continued until 2 weeks post-therapy. Silver sulfadiazine was started at the occurrence of grade 1 radiation dermatitis. The Silver-nylon group RTOG scores at the end of radiation treatment were significantly lower than the silver sulfadiazine group (1.67 vs. 2.53, $p= 0.01$). The silver-nylon group also had fewer and shorter breaks in treatment than the control group (16).

Studies in head/neck cancer and breast cancer have yielded less clear results because of methodologic flaws. Vavassis et al (17) evaluated silver-nylon dressings in 12 patients with squamous carcinoma of the head and neck undergoing radiation therapy. Silver-nylon dressings were placed on one side of the neck and silver sulfadiazine on the contralateral side of the neck. Silver-nylon dressings and silver sulfadiazine were initiated at the point where radiation dermatitis was assessed as RTOG grade 2 or greater. Nine of the 12 patients developed radiation dermatitis of RTOG grades 3 or 4. There was no difference in improvement in RTOG grade between control (silver sulfadiazine) and silver-nylon sides. Pain control was subjectively better in the silver-nylon side for 8 of 12 patients. Furthermore, half (6/12) of the patients stopped using silver sulfadiazine and applied silver-nylon to both sides of the neck because of better pain control.

Aquino-Parsons et al (8) studied silver-nylon dressings in 196 breast cancer patients undergoing radiation therapy of either 42.5 Gy in 16 fractions over 22 days or 45 Gy in 25 fractions over 33 days with a boost dose to the tumor bed. The experimental arm used silver-nylon dressings on the inframammary fold continuously placed except during radiation therapy and bathing, starting at day 6 of radiation therapy and continuing until 14 days after completion of therapy. The control group used twice-daily application of moisturizing cream (with brand chosen by the patient), along with topical steroids for pruritis or brisk erythema, and saline compresses, hydrogel or silver sulfadiazine for moist desquamation. Moist desquamation occurred in 38% of patients with no difference in incidence, size or RTOG score of moist desquamation between treatment and control arms. Patients reported less itching in the silver-nylon arm at completion of the course of radiation therapy and at one week afterwards. The methodologic flaws of this study included withholding treatment until day 6 of radiation therapy and using the silver-nylon dressing only on the inframammary fold rather than on the entire radiated field.

Based on US Military experience and utility for multiple injury conditions, the Department of Health and Human Services / Biomedical Advanced Research and Development Authority (BARDA) has placed Silverlon® in the National Stockpile, and, since 2013, has funded multiple preclinical studies to broaden FDA-cleared indications for mass-casualty use. In July, 2019, Silverlon® obtained the first-ever FDA clearance for the treatment of sulfur-mustard chemical weapons burns. BARDA and Argentum maintain an active research program seeking FDA clearance for radiation injuries including porcine preclinical studies of cutaneous radiation syndrome. The present study, part of the BARDA radiation effort, seeks to perform clinical studies leading to FDA clearance for the indication of radiation dermatitis. Our previous research in multiple animal models (rat, hairless guinea pig, Gottingen minipig), multiple wound types (thermal burns, chemical burns and open wounds), and several different wound depths (superficial partial thickness, deep partial thickness and full thickness) demonstrate that there is no adverse or systemic effect of topical silver nylon therapy. In all animal studies, following extended application of Silverlon® dressings, silver ion was not detectable in blood, spleen, liver or kidney samples obtained at autopsy. (18,19) The present study, a small human safety study of topical application of silver-nylon dressings to patients undergoing radiation therapy, is intended to complete our extensive safety experience with silver nylon dressings in support of an FDA 510(k) application for the additional indication for human radiation dermatitis.

1.3. OBJECTIVES

Primary Objective: To investigate the safety of Silverlon® dressing in patients throughout their prescribed course of radiation therapy and after radiation therapy.

- *Hypothesis:* We do not expect any adverse effects from extended use of Silverlon® dressing during and after radiation therapy.
- *Primary Outcome Measures:* Adverse reactions/events documented by the radiation oncologist as "probable" or "definite" related to Silverlon® Dressing (Weekly AE/Chart Review Source Doc).

Secondary Objective: To evaluate the feasibility of managing radiation dermatitis with Silverlon® dressing.

- *Hypothesis:* We expect that Silverlon® will be a feasible therapeutic modality for managing radiation dermatitis. We expect high compliance rate during RT and slightly lower when skin symptoms are not presented (i.e., before RT and post-RT). We do not expect any withdrawals due to adverse reactions to the dressing.
- *Secondary Outcome Measures:* Compliance; Withdrawal rate due to dressing.

Exploratory Objective: To monitor the severity of radiation dermatitis and patient quality of life during use of Silverlon® dressing throughout radiation therapy and after radiation therapy.

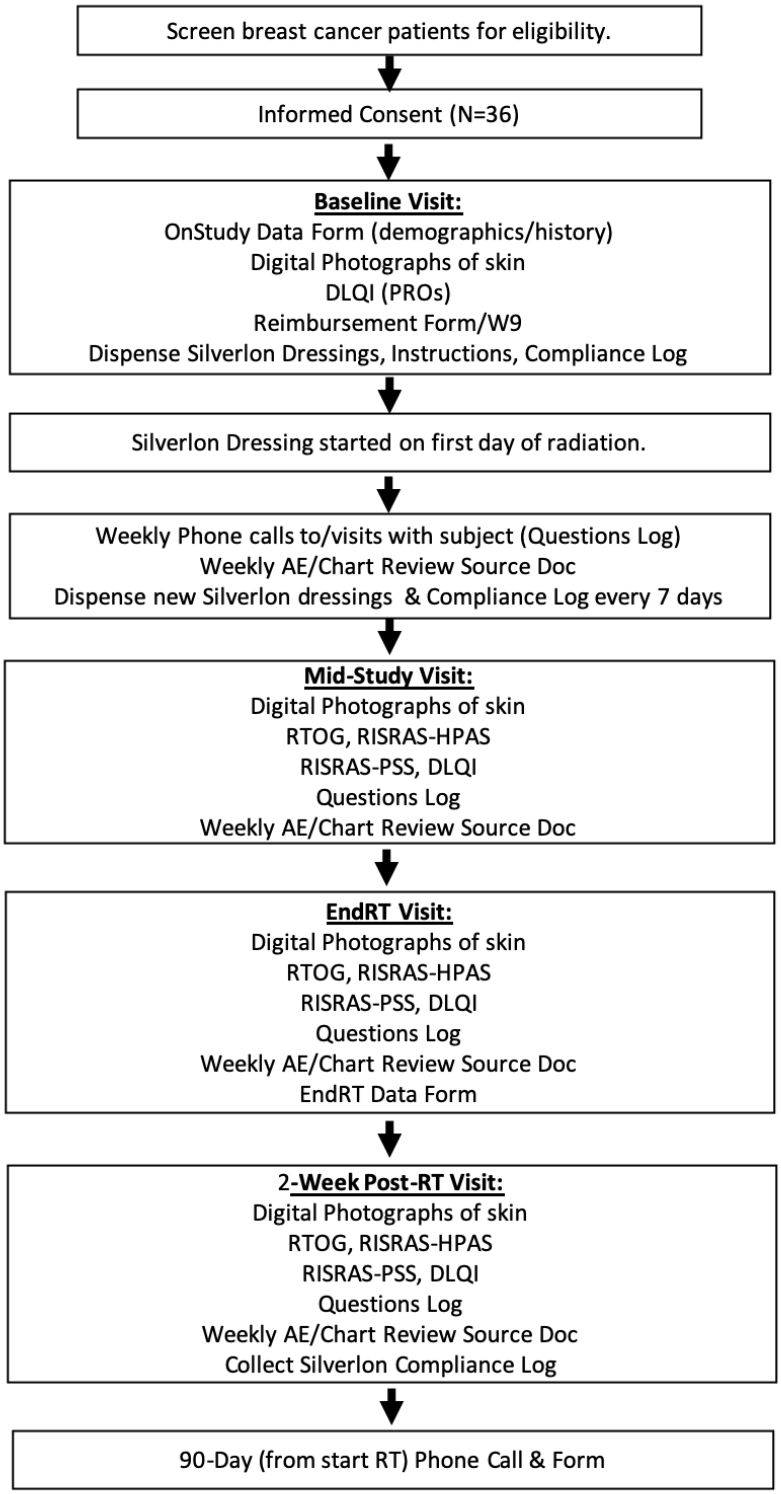
- *Exploratory Outcome Measures:* radiation dermatitis severity (RTOG Score & Radiation Induced Skin Reaction Assessment Scale (RISRAS)); DLQI

2. STUDY DESIGN

2.1. OVERVIEW

This is a single-site, non-blinded, non-randomized safety study of patients undergoing radiation therapy for breast cancer. This safety study will be conducted by University of Rochester Medical Center in the Departments of Dermatology & Radiation Oncology. Radiation therapy treatment will be delivered at The University of Rochester Medical Center. The study will not address radiation dose, scheduling or application method, which will remain the province of the attending radiation oncologist. The single intervention will be the application of Silverlon® dressing over the radiation site (i.e., whole irradiated breast area) which will start on the first day of radiation therapy and continue for 2 weeks after completion of radiation therapy. The patients will wear the Silverlon® dressing all of the time, except while bathing/showering and during radiation therapy sessions. All study visits and evaluations will take place at times already scheduled for radiation therapy and will not involve additional travel solely for research purposes. Subject participation will start just prior to the start of their prescribed course of radiation therapy and will be completed 2 weeks following completion of radiation therapy. There are no control or placebo groups.

2.2. STUDY SCHEMA



3. CHARACTERISTICS OF RESEARCH POPULATION

3.1. NUMBER OF SUBJECTS

This is a single site study at the University of Rochester Medical Center, with an accrual goal of 30 fully evaluable subjects. "Fully evaluable" as defined as completing informed consent, meeting eligibility criteria, initiating Silverlon® dressing during radiation therapy and continuing to two weeks after completion of radiation therapy. Therefore, the 30 fully evaluable subjects must complete full protocol procedures. Assuming a 20% withdrawal rate, we will recruit 36 eligible subjects. Subjects who initiated treatment but withdraw from the study will be used in the intent to treat analyses. In the past year, the Wilmot Cancer Institute had 75 patients that would be eligible for this study which demonstrates our ability to reach our accrual goal. To reach this goal of 30 fully evaluable subjects, the total number of subjects approached and/or consented may reach 75 subjects.

PARTICIPANT POPULATION(S)

Accrual Number:	**Category/Group:** (Adults/Children Special/Vulnerable Populations)	**Consented:** Maximum Number to be Consented or Reviewed/Collected/ Screened	**Intent to Treat:** Number to enroll and initiate treatment.	**Fully Evaluable:** Number to enroll and fully complete study.
Local	75/0/0	75	36	30
Study-wide	75/0/0	75	36	30
Total:	75/0/0	75	36	30

3.2. GENDER OF SUBJECTS

Subjects must be female. Approximately 99% of breast cancer diagnoses occur in adult women. Since too few men are diagnosed with the disease to allow meaningful sub-group analyses, subject accrual will only be women (≥ 22 years of age) with breast cancer. Additionally, men are unlikely to wear a bra and the dressing would have to be held in place using another method, which is not the purpose of this study.

3.3. AGE OF SUBJECTS

This study will enroll adult patients (22 years of age or older). There is no upper age limit for participation in this study. There will be no children enrolled in this study.

3.4. RACIAL AND ETHNIC ORIGINS

There are no restrictions based on race or ethnicity in this study. Based upon an ethnic minority population of 16% in the six-county area of Rochester, we expect Rochester accruals to be at least 12% minority.

3.5. INCLUSION CRITERIA

- Females, 22 years of age or older (i.e., adult and elderly), with diagnosis of primary breast cancer (excluding inflammatory and medullary breast cancers).
- Scheduled to receive short-course external beam radiation therapy (i.e., 2.0-3.0 Gy for 15-20 fractions) or conventional external beam radiation therapy (i.e., 1.8-2.0 Gy for 25-40 fractions), with or without boost dose, to the whole breast. Chest wall irradiations are eligible. Bolus and IMRT are permitted. Lymph node irradiation (i.e., internal mammary nodes, supraclavicular nodes, axillary nodes, etc.) as part of their prescribed radiation therapy are permitted. Radiation therapy regimens eligible for study are described in table below:

	WHOLE BREAST	**BREAST BOOST**	**TUMOR BED = WHOLE BREAST +/- BOOST**	**LYMPH NODES**
MIN TOTAL DOSE	35 Gy	10 Gy	50.0 Gy	45 Gy
MAX TOTAL DOSE	50.4 Gy	16 Gy	66.0 Gy	50.4 Gy
MIN DOSE PER FRACTION	1.8 Gy	2.0 Gy	1.8 Gy	1.8 Gy
MAX DOSE PER FRACTION	3.0 Gy	2.5 Gy	3.0 Gy	2.0 Gy
MIN # OF FRACTIONS	15	5	15	15
MAX # OF FRACTIONS	30	10	40	30

- Subject may have had chemotherapy prior to radiation. A minimum of two weeks is required between the end of chemotherapy and start of radiation therapy.
- No history of previous breast or chest radiation therapy.
- Subject may or may not have had surgery (lumpectomy or mastectomy) prior to RT. (Note: Surgery is not required for eligibility).
- Subjects may be currently prescribed and receiving hormonal therapy or agents used to treat Her2-nue positive cancer (e.g., Herceptin, Kadcyla, etc).
- Subjects must be able to read, speak, and understand English language (all study forms are in English).
- Subjects must be able to give informed consent.
- Subjects must be willing to have photographs taken of radiation-induced skin changes in the radiation treatment area.
- Subjects must be willing to wear Silverlon® dressing and undergarment (i.e., bra) at all times, except when bathing/showering and during their radiation therapy session.
- Subjects must be willing to complete a Silverlon® Compliance Log to document the date and time that Silverlon® was removed and applied each day during the study.

3.6. EXCLUSION CRITERIA

- Diagnosis of medullary or inflammatory breast cancer.
- Diagnosis of tumors of the breast other than primary breast cancer (skin cancers, lymphomas, or metastatic cancers from other primary sites).
- Partial breast irradiation (PBI) treatment technique is not eligible.
- Concurrent chemotherapy or systemic therapies, except for hormonal therapies and agents for Her2-neu-positive cancers (as described in inclusion criteria).
- Pregnant or planning to become pregnant. Pregnant females are ineligible because pregnancy is a contraindication for RT. All subjects of childbearing potential will be asked if they are pregnant or could be pregnant. The subject must respond "no" to continue with radiation and to participate in this clinical study.
- Previous radiation to the chest or breast.
- Radiation being given for palliative purposes.
- Presence of unhealed surgical wounds, biopsy sites, open wounds in the breast or chest area.
- Presence of breast infection.
- Subjects currently on anti-EGFR (human epidermal growth factor receptor) therapy, such as Iressa® (gefitinib) or Erbitux™ (cetuximab, C225).
- Previous diagnosis of autoimmune disease, connective tissue disease, or radiosensitivity disorder.
- Presence of any active dermatological issues in radiation treatment area (i.e., fungal skin infection, dermatitis, psoriasis plaques, etc.).
- Chronic skin disease of the breast, previous breast trauma or scarring of the breast
- Subjects with known sensitivity to silver or nylon.
- Subjects unable or unwilling to wear Silverlon® dressings and undergarment (i.e., bra) at all times, except while bathing/showering and during their radiation therapy session.
- Subjects unable to speak, read, or understand English language (all study forms are in English).

3.7. WOMEN & CHILDREN

This study will enroll women (adult and elderly). Approximately 99% of breast cancer diagnoses occur in adult women. Since too few men are diagnosed with the disease to allow meaningful sub-group analyses, subject accrual will only be women (≥ 22 years of age) with breast cancer. This study will not enroll children because breast cancer is primarily a disease diagnosed in adult women above the age of 21.

3.8. VULNERABLE POPULATIONS

There will be no members of special or vulnerable populations enrolled in this study.

3.9. TARGETED ENROLLMENT

This study will accrue 30 fully evaluable subjects. Assuming a 20% withdrawal rate, we will recruit 36 eligible subjects. To reach this goal of 30 evaluable subjects, the total number of subjects approached and/or consented may reach 75 subjects. In the past year, the Wilmot Cancer Institute had 75 patients that would be eligible for this study which demonstrates our ability to reach our accrual goal. Demographics of the enrollment population has been estimated from prior University of Rochester studies drawing from a typical patient population being treated at the Wilmot Cancer Institute. This information is provided in the following table to illustrate an anticipated patient population profile for 75 enrolled subjects at the study site.

Racial Categories	Ethnic Categories			
	Not Hispanic or Latino	Hispanic or Latino	Unknown Ethnicity	Total
	Female	Female	Female	Female
American Indian/Alaska Native	0	0	0	0
Asian	4	1	0	5
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	9	0	0	9
White	51	3	3	57
More Than One Race	0	1	0	0
Unknown Race	1	0	3	4
Total	64	5	6	75

4. SUBJECT IDENTIFICATION, RECRUITMENT, AND CONSENT

Patients with breast cancer referred for radiation therapy will be screened through the electronic medical record (EMR) at the University of Rochester Medical Center by study personnel. Study personnel will notify the treating radiation oncologist of the eligible patients. Alternatively, study personnel will be notified of eligible patients at radiation oncology team meetings. At the patient's CT-SIM appointment or another clinic visit in Radiation Oncology prior to the start of radiation therapy, the radiation oncologist will ask the patient if they are interested in hearing about participation in a clinical research study. Subjects must be consented at prior to the start of radiation therapy. The Silverlon® dressing used in this study must be applied to the whole breast area that will receive radiation two days prior to the start of radiation therapy.

If the patient agrees, study personnel will meet with the patient in a meeting room or clinic room for discussion of the study with minimal disturbances. All study materials are in English, therefore all subjects must be able to read, speak, and understand English. Current FDA, ICH, NCI, state, federal, and institutional regulations concerning informed consent will be followed.

The patient will be informed that we are conducting a study and would like to invite them to participate. The study personnel will go over the study procedures and the informed consent form. The patient will have time to ask questions, take the consent form home, and discuss with family members. The patient will be informed that participation in the study will in no way influences their prescribed course of treatment and care at the University of Rochester Medical Center. If the patient needs time to consider participation, the study personnel will follow-up with them by phone the next day. Alternatively, if the patient has limited time to meet with study personnel, the patient will be given an informed consent form to take home with them and the study personnel will then then contact the patient by phone the next day to discuss their interest

in study participation. By phone, the patients will be informed that we are conducting a study and would like to invite them to participate. The patient will be offered an in-person meeting, where she is allowed to bring a companion. The study personnel can discuss the study by phone if the patient requests more information; however, the in-person meeting is required for obtaining informed consent. The informed consent form will include consent for photographs of the skin in the radiation treatment area. The photographs will be de-identified if used in publications related to this study. There will be a provision on the informed consent form for the patient to opt-out of publication of photographs. However, patients declining consent for photographs for research purposes will be deemed ineligible for this study.

If the patient agrees to participate, the patient will sign and date the informed consent, along with the study personnel obtaining consent. A copy of the signed consent form will be given to the patient to take home and the original signed consent form will be placed in the subject's study folder. An **Eligibility Checklist** containing inclusion and exclusion criteria will be completed and signed by study personnel and placed in the subject's study folder. A unique numerical Study ID will be given to each study subject, which will be included on all forms along with the subject's initials. This will help de-identify the forms used for data collection and the electronic database. Additionally, during the consent process, subjects will be asked to complete a W9 form for reimbursement purposes. The subject will provide their name, mailing address, and signature on the Study Reimbursement Form to ensure that reimbursement can be mailed to her after study participation has completed.

The consent process will be free of coercion and undue influence. Study personnel will then explain the project to the potential subjects and answer all questions. The subject will be provided sufficient information and time make a thoughtful and rational decision on participation. The subject will be given the opportunity to take the consent form home for review and discussion with family members before finalizing her decision. After informed consent form is signed, subjects will be given a copy of the document, along with the phone numbers of the study personnel to call if they have further questions. The completed informed consent forms will be kept in the subject's study folder and stored in a locked office in a locked cabinet.

4.1 REMOTE CONSENT PROCEDURES

Remote informed consent will be allowed using the following steps:

During an initial in-person or telemedicine meeting with the patient, the study will be discussed with the patient by qualified personnel. If the patient expresses interest in the study, a full RSRB-approved consent form will be provided to the patient. This discussion will be documented in eRecord. If the study was initially discussed at a telemedicine visit, a copy of the RSRB-approved consent form will be provided to the patient via standard mail or e-mail, per patient preference. An RSRB-approved patient letter containing the instructions for remote consenting will be included.

If the patient was seen in-person, a paper copy of the RSRB-approved consent form will be provided at the time of the in-person visit, along with a copy of the RSRB-approved patient letter containing instructions for the remote consent process. Since the next clinic visit for many patients who are consulted via telemedicine may be the start of treatment, this option is provided to reduce the need for patients to return to the clinic solely for the purpose of signing the consent form.

A discussion between the patient and the provider will occur after the patient has reviewed the consent form. The provider will review the scope of the subject's participation in the study, and address any questions or concerns that the subject may have. This discussion can occur in-person, over the phone, or as a telemedicine visit. The discussion of the study and any questions patient had must be documented in an eRecord note, in addition to the patient's decision about study participation. Documentation of patients decision regarding participation also must be documented in eRecord

The patient must return a copy of the signed consent via e-mail, standard mail, or other electronic method prior to enrollment. Patient should return original signed to clinic at the next onsite visit, or via standard mail using pre-addressed and stamped envelopes that will be provided by study staff. In the event the patient does not provide the original consent, a new one will be signed at the next visit. The consenting MD will sign both the copy returned by the patient immediately and also the original copy, once the patient has returned the original copy to the clinic. The date written by both the patient and the consenting provider is to be the date the documents are actually signed by the respective individuals, even if these dates do not match. A copy of the consents signed by both the subject and the MD will be provided to the subject.

5. METHODS AND PROCEDURES

5.1. STUDY PROCEDURES

The majority of study procedures will relate to their course of radiation therapy. The dose, scheduling and duration of radiation therapy will be determined by the attending radiation oncologist and are outside of the purview of this study. All study visits will take place at the time of scheduled radiation therapy sessions and will not involve additional travel.

To ensure appropriate safety precautions when conducting in-person study procedures, the process for conducting in-person visits outlined in the Guidance for Human Subject Research will be followed.

- Study personnel will keep track of all patients that are eligible for the study, all patients approached about the study, and the outcome of that discussion (Declined participation or Consented). For patients that declined participation, study personnel will indicate the reason for decline. All of this information will be entered into the electronic REDCap **Screening Log** for the study.

- **Baseline Visit (after consent):**
  - Study personnel will obtain demographic and lifestyle information from the subject to complete the OnStudy Data Form. This information will include: age, gender, race, ethnicity, marital status, smoking status, alcohol use, prescription opioid use, and breast size (i.e., bra size), and if they had breast reconstructive surgery before radiation therapy. This form can be completed electronically in REDCap or on paper and then entered into REDCap.
  - The subject will complete a Study Reimbursement Form and W9 to receive their payment at the end of the study for participation.
  - Study personnel will take baseline digital photographs of skin in radiation treatment area (i.e., where the Silverlon® will be applied).
  - The subject will be asked to complete a paper questionnaire, Dermatology Life

Quality Index (DLQI). This will provide baseline quality of life and symptoms for the subject prior to the start of RT and Silverlon® Dressing. Study personnel will electronically enter the data from the form into REDCap for secure storage in the study database.

- Study personnel will review the Silverlon® Dressing Patient Instructions with the subject thoroughly to ensure the subject understands the application, use and, storage of the Silverlon® dressing. It is important for the subject to follow the Silverlon® Dressing Patient Instructions instead of the package insert for the use of Silverlon dressing during radiation therapy and this study. The patient instruction sheet will be given to the subject with the dressings. Study personnel will show the subject how to wear the Silverlon® dressing in their bra to cover the whole breast that will be irradiated. The subject will be given two Silverlon® dressings of the appropriate size necessary to cover the whole irradiated breast. The subject will be instructed to wear the Silverlon® Dressing in their bra to cover the whole irradiated breast at all times except bathing/showering and during radiation therapy sessions. The subject will be instructed to start wearing the Silverlon® Dressing on the first day of radiation therapy. The subject will be instructed that they will receive two new Silverlon Dressings every 7 days from study personnel. Subjects will be instructed to use the same dressing for 7 days. Subjects will be instructed that if the dressing becomes soiled (i.e., dirty, odor, stain, spill, etc.) for any reason, they can change it to the second dressing and they should record this change in their Compliance Log. *(NOTE: The first Silverlon dressings can be given to the subject prior to the first day of radiation therapy or on the first day of radiation therapy.)*
- Study personnel will instruct subjects that moisturizing lotions or other topical agents should not be applied to the whole breast area or used with the Silverlon dressing. However, subjects may apply moisturizing lotions or other topical agents to irradiation sites outside of the whole breast area that are not covered by Silverlon dressing. Use of topical agents while on study may be permitted in certain circumstances under the guidance of the treating physician and in accordance with Sections 5.2 and 6.0.
- The subject will also be given a **Silverlon® Compliance Log** to document each time they remove the Silverlon® dressing and put the Silverlon® dressing on. Study personnel will write the Subject ID, Subject Initials (First, Middle, Last (FML)) on the top of each page of the Compliance Log. Study personnel will write the date the Log was given to the subject in "Log Start Date" and write the date the Log was returned in "Log End Date". The "Log End Date" should correspond with the date that new Silverlon® dressings and new Log are dispensed to the subject (i.e., every 7 days).
- It is anticipated that Baseline Visits will involve 30 minutes or less of the subject's time. This is a paper form that the subject will take home with them and complete as necessary daily whenever the Silverlon® dressing is removed and put back on.
- Additional Silverlon® Dressing will be provided to the subject every 7 days during the trial. A new Compliance Log will be given to the subject with two new Silverlon® Dressing every 7 days. For compliance reasons, subjects will return the used Silverlon® dressings and the completed Compliance Log to study personnel every 7 days when new dressings and log are dispensed.

- Study personnel will complete additional information on the **OnStudy Data Form** using an EMR chart review to obtain demographic and medical history information: history of present illness, Tumor stage and TNM classification of breast cancer, body mass index (BMI), breast size, past medical history, body mass index, Fitzpatrick classification, previous chemotherapy or immunotherapy for breast cancer, prior surgery for breast cancer, and current medications.

- **Weekly during RT:** During RT, the subject will have a scheduled clinic visit with their treating radiation oncologist. During this visit, the radiation oncologist will document the absence or presence of any adverse reactions/adverse events in their EMR chart note. Study personnel will review the EMR Chart note for documentation and description of the adverse reaction/event, intensity, relationship to Silverlon® dressing, action with Silverlon® dressing, treatment provided for reaction/event, and the outcome of reaction/event. Study personnel will electronically enter the data from the form into REDCap for secure storage in the study database. Study personnel may also be present at the weekly scheduled clinic visit to capture any AE-related information. The information will be entered into the **Weekly AE/Chart Review Source Doc**, which is an electronic REDCap form. Study personnel will enter any documented any adverse reactions, skin changes, and/or radiation treatment changes in the form.

- Study personnel will arrange to meet the subject every 7 days to provide to new Silverlon® dressings and **Silverlon® Dressing Patient Instructions.** This will occur until the subject completes the study. Study personnel will complete the **Silverlon® Accountability Log** to document the Subject ID, date, size, and number of Silverlon® dressings dispensed to each subject. This log will keep track of the amount of Silverlon® dressing on site in at University of Rochester. The investigator will contact Argentum if more Silverlon® dressings are needed.

- **Weekly Phone Calls or Visits during RT:** Study personnel will contact the subject by phone, email, or in clinic (as preferred by the subject) to ask the following 4 questions: 1) if they are wearing Silverlon® while sleeping; 2) having any discomfort while wearing Silverlon®; and 3) having any adverse reactions to the Silverlon®; if they feel Silverlon® is helping their skin. This information will be entered into an electronic REDCap form called the **Questions Log.** If the subject cannot be reached by phone, with prior permission a voicemail message will be left with the subject to return the phone call. The study personnel will follow-up with the subject within 24 hours by phone (or preferred mode of contact). All phone calls will be documented in the electronic **Comprehensive Study Log**. Study personnel may also meet with the subject in clinic during their scheduled radiation treatment appointment.

- **Mid-Study Visit**: This visit will occur at the subject's scheduled mid-treatment clinic visit with their radiation oncologist. Study personnel will meet with the subject with or after the radiation oncologist at this visit. Subjects will be reminded of this study visit at the phone call the previous week.

    - The radiation oncologist will clinically assess the radiation-induced skin reaction in the breast area that Silverlon® dressing was applied. The radiation oncologist will rate the skin using the **RTOG scale** and the **RISRAS-Healthcare Professional Assessment Scale**. These ratings will be completed electronically in on a tablet (in REDCap).
    - The subject will complete two surveys that contain: **Dermatology Life Quality Index (DLQI) and RISRAS-Patient Symptom Scale.** The subjects will be asked to complete these forms by focusing on the whole breast to which the Silverlon® dressing has been applied. These surveys will be completed electronically on a tablet (in REDCap).
    - **Digital photographs** of the skin in the radiation treatment area (where the Silverlon® dressing has been applied) will be taken.
    - Study personnel will also ask the subject: 1) if they are having any adverse reactions to wearing Silverlon®; 2) if they are wearing Silverlon® while sleeping; 3) having any discomfort while wearing Silverlon®; and 4) if they feel Silverlon® is helping their skin. This information will be entered electronically into the **Questions Log**.
    - Study personnel will also complete the **Weekly AE/Chart Review Source Doc** at this visit to document any adverse reactions, skin changes, and/or radiation treatment changes.
    - This visit is estimated to involve 10 minutes of less of the patient's time.

- Completion of Radiation Therapy Visit (EndRT Visit): This visit will be scheduled with the subject at their scheduled last radiation treatment. Study personnel will meet with the subject with or after the radiation oncologist at this visit. Subjects will be reminded of this study visit at the phone call the previous week.

    - The radiation oncologist will clinically assess the radiation-induced skin reaction in the breast area that Silverlon® dressing was applied. The radiation oncologist will rate the skin using the **RTOG scale** and the **RISRAS-Healthcare Professional Assessment Scale**. These ratings will be completed electronically in on a tablet (in REDCap).
    - The subject will complete two survey forms that contain: **Dermatology Life Quality Index (DLQI) and RISRAS-Patient Symptom Scale.** The subjects will be asked to complete these forms by focusing on the whole breast to which the Silverlon® dressing has been applied. These surveys will be completed electronically on a tablet (in REDCap).
    - **Digital photographs** of the skin in the radiation treatment area (where the Silverlon® Dressing has been applied) will be taken.
    - Study personnel will also ask the subject: 1) if they are having any adverse reactions to wearing Silverlon®; 2) if they are wearing Silverlon® while sleeping; 3) having any discomfort while wearing Silverlon®; and 4) if they feel Silverlon® is helping their skin. This information will be entered electronically into the **Questions Log**.
    - Study personnel will also complete the **Weekly AE/Chart Review Source Doc** at this visit to document any adverse reactions, skin changes, and/or radiation treatment changes.
    - Study personnel will remind the subject to continue wearing Silverlon® Dressing for two additional weeks (i.e., 14 days).
    - This visit is estimated to involve 10 minutes of less of the patient's time.

- Study Personnel will perform an EMR chart review to obtain final radiation therapy information for the subject: positioning (prone vs. supine), total radiation dose, fractionation, boost dose (if any), bolus (if used), any delay in RT, any documented clinical complications, skin changes, or treatment changes. This information will be entered into the **EndRT Data Form**. This form can be completed electronically in REDCap or on paper and then entered into REDCap.

- Study personnel will contact the patient by phone (or preferred method of contact) at least 48 hours prior to their scheduled 2-week Post-RT Visit to remind them of the visit. All phone calls will be documented in the electronic **Comprehensive Study Log.**

- **2-Week Post-RT Visit:** This visit will be scheduled with the subject at their scheduled last radiation treatment. Study personnel will meet with the subject with or after the radiation oncologist at this visit. Subjects will be reminded of this study visit at the phone call the previous week.
    - The radiation oncologist will clinically assess the radiation-induced skin reaction in the breast area that Silverlon® dressing was applied. The radiation oncologist will rate the skin using the **RTOG scale** and the **RISRAS-Healthcare Professional Assessment Scale**. These ratings will be completed electronically in on a tablet (in REDCap).
    - The subject will complete two survey forms that contain: **Dermatology Life Quality Index (DLQI) and RISRAS-Patient Symptom Scale.** The subjects will be asked to complete these forms by focusing on the whole breast to which the Silverlon® dressing has been applied. These surveys will be completed electronically on a tablet (in REDCap).
    - **Digital photographs** of the skin in the radiation treatment area (where the Silverlon® Dressing has been applied) will be taken.
    - Study personnel will also ask the subject: 1) if they are having any adverse reactions to wearing Silverlon®; 2) if they are wearing Silverlon® while sleeping; 3) having any discomfort while wearing Silverlon®; and 4) if they feel Silverlon® is helping their skin. This information will be entered electronically into the **Questions Log**.
    - Study personnel will also complete the **Weekly AE/Chart Review Source Doc** at this visit to document any adverse reactions, skin changes, and/or radiation treatment changes.
    - Study personnel will collect the final **Compliance Log** and used Silverlon® Dressings from the subject.

- **90-day Follow-Up:** This follow-up by phone call, MyChart message or paper mail will occur 90 days from the start of RT and be scheduled with the subject at their 2-week Post-RT Visit. One or all three methods will be used to contact the subject as needed to complete the follow-up. Message text for copy/paste into MyChart has been included in Appendix A. For completion of the follow-up by paper mail, a pre-addressed and stamped envelope will be provided for the return of the paper response. For safety assessment, FDA recommends following patients up to 90 days. Study personnel will contact the subject to document an adverse reactions or skin reactions in the radiation treatment area to which Silverlon dressing was applied. Study personnel will ask the following questions: 1) Since your 2-Week Post-RT visit, has your skin reaction in the area where the Silverlon® dressing was applied improved, stayed the same, or worsened?; 2) Do you have any skin pain in the area where the Silverlon® dressing was applied? (yes/no); 3) Do you have any itching in the area where the Silverlon® dressing was applied? (yes/no); 4) Do you feel like your skin in the radiation treatment area has fully recovered? (yes/no); and 5) Would you recommend Silverlon® dressing to other patients during radiation therapy? (yes/no). For question 1, if the subject answers “worsened”, study personnel will document the description of the skin reaction and notify the treating radiation oncologist to follow-up with the subject.

5.2. SILVERLON® DRESSING

The device being evaluated is Silverlon® Burn/Wound Contact Dressings. The device has been commercially marketed since 2003 and has 16 FDA 510(k) clearances. Silverlon® has been used on hundreds of thousands of patients over the last 17 years. For this reason, the intervention is considered a non-significant risk device. This study is being conducted to provide safety data to the FDA to support an application to specify a radiation dermatitis indication for Silverlon® Dressings. For this study, Silverlon® Dressing will be supplied by Argentum Medical. Where possible, all product will come from a single lot. Product will be sent directly to the study coordinator or principal investigator at University of Rochester Medical Center. On conclusion of the study, any unused product will be returned to Argentum Medical. Study personnel will be responsible for storage and distribution of the Silverlon®. Storage will follow manufacturer's instructions which are: "Store Silverlon® Burn/Wound Contact Dressings in normal warehouse conditions. Keep dry. Avoid excessive heat or humidity (20). Each patient will receive the appropriate size of Silverlon® to cover the whole irradiated breast area. Subjects will receive two Silverlon® dressings at the start of the study. Since, Silverlon® dressings are indicated for use up to 7 days, two Silverlon® dressings will be dispensed to the subject every 7 days until completion of the study (i.e., 2 weeks (14 days) post-radiation therapy). The total number Silverlon® dressings dispensed to subjects will vary and be based on the length of their prescribed course of radiation therapy. Furthermore, additional Silverlon® dressing will be dispensed to the subject by request (i.e., due to loss, damage, ran through washing machine, etc.) as necessary for them to complete the study.

For this study, each subject will be instructed to wear the Silverlon® dressings for 7 days in the following manner:

- Silverlon® dressing should cover the whole irradiated breast area and kept in place by a bra.
- Start wearing Silverlon® dressing on the first day of radiation therapy
- Continue wearing until 2 weeks after completion of radiation therapy.
- Wear Silverlon® dressing all of the time except when bathing/showering, swimming, and during radiation treatment sessions. The dressing should be stored in a clean, dry resealable bag or container (e.g., ziplock bag) when not worn to protect it from becoming soiled of damaged.
- The radiation site can be washed daily with mild unscented soap (per instructions by the radiation oncologist).
- Use of any topical ointments, lotions, creams or gels with Silverlon® dressing during the course of the study is permitted under the guidance of the treating physician for subjects with worsening skin reactions to help prevent moist desquamation and subject withdrawal.
    - Silverlon® dressing is to be removed during the application of topical agents to the treatment area, and re-applied after total absorption of the topical agent into the skin (approximately one hour after application). Documentation of removal and re-application of the Silverlon® dressing in the Subject Compliance Log for topical medication administration is required.
- Do not use Silverlon® dressing past expiration date on the product packaging.

5.3. OUTCOME MEASURES AND STUDY FORMS

Eligibility Checklist: This paper form contains the inclusion and exclusion criteria for participation in this study. This form is completed to ensure eligibility for the trial. Study personnel obtaining consent will complete this form.

Screening Log: This electronic REDCap form will be used to document the eligibility of subjects, if the subject consented or declined participation, and reason for declining participation. The Screening Log will help create a CONSORT diagram at the completion of the study. This form will electronically capture screening information for the study and submit the information directly to the secure REDCap database at the University of Rochester Medical Center. Study personnel will access the form electronically through REDCap.

Study Reimbursement Form: This paper form is required along with a signed W9 for reimbursement of the adult caregiver in this study. The address on this form must match the signed W9 completed by the subject at the start of the study. After the consent process is completed, the subject (i.e., will print their name, mailing address, sign, and date this form, as well as complete a W9 form. At the end of the subjects' participation, the study coordinator or PI will circle the appropriate number of visits completed, indicate the number of visits completed, and indicate the amount to be reimbursed. A total of $200 will be reimbursed for completion of all study procedures.

OnStudy Data Form: This is an electronic REDCap form that captures demographic information and medical history information on each subject. This form will be completed on paper or electronically and submit information directly to the secure REDCap database at the University of Rochester Medical Center. If completed on paper, the data will be entered into REDCap by study personnel. This form will collect the following:

- Subject ID
- On Study Date (Consent Date)
- Subject Initials
- Subject's First Name
- Subject's Last Name
- Subject's MRN
- Contact phone number
- Contact email (if preferred)
- Location of Radiation Therapy (Greece, WCI/SMH, Pluta)
- Age
- Race
- Ethnicity
- Marital Status
- Smoking status
- Alcohol use
- Prescription opioid use
- Breast size (i.e., bra size)
- Breast reconstructive surgery (yes/no)
- Tumor Stage (DCIS, I, II, III, IV)
- Chemotherapy Prior to Radiation (yes/no)
- Current hormone treatment (yes/no)
- Current Herceptin treatment (yes/no)
- Body Mass Index (BMI)
- Fitzpatrick Skin Type
- Surgery before RT (yes/no)
- Current Medications

Weekly AE/Chart Review Source Doc: This is an electronic REDCap form for collection of any radiation treatment changes, skin changes, or adverse reactions documented by the treating radiation oncologist in the EMR chart note for the patient's weekly clinic visit. Study personnel will review the EMR chart note and report any documented any adverse reactions, skin changes, and/or radiation treatment changes in the form. The following information will be collected on the form:

- Changes in prescribed radiation treatment (yes/no; if "yes", then description of change)
- Documentation of skin changes in radiation treatment area (yes/no)
- Occurrence of adverse event in radiation treatment area to which Silverlon® dressing was applied
- Description of the adverse event
- Date of onset
- Serious (Yes/No)
- Intensity (Mild/Moderate/Severe)
- Relation to Study Drug (Definite/Probable/Possible/Unlikely/Unrelated)
- Action with Study Drug (No Action/Interrupted/Stopped Entirely).

Questions Log: This log will be an electronic REDCap form that collects the answers to the questions asked to the patient by phone, email, or in study visits (as preferred by the subject). Study personnel will ask the subject: 1) Are you wearing Silverlon dressing while you are sleeping? (yes/no); 2) Are you having any discomfort while wearing the Silverlon dressing? (yes/no); and 3) Are you having any adverse reactions to the Silverlon dressing? (yes/no). If the subject answers "yes" to question 3 regarding an adverse reaction to Silverlon, study personnel will document a description of this reaction in the space provided on the form.

RTOG Score: The RTOG toxicity criteria is one of the most commonly used scales for radiation-induced skin reactions (21, 22). The radiation oncologist will rate the skin reaction in the area where Silverlon® dressing was applied in person using the RTOG scale below. The RTOG scores will completed on paper and then entered electronically into REDCap:

RTOG SCALE

0	1	2	3	4	5
No change	Faint erythema, dry desquamation, epilation, decreased sweating	Tender or bright erythema, moderate edema, patchy moist desquamation	Confluent moist desquamation in areas other than in skin folds, pitting edema	Ulceration, hemorrhage, necrosis	Death

Radiation Induced Skin Reaction Assessment Scale (RISRAS): This scoring system contains both a healthcare professions assessment scale and a patient symptom scale (23). The healthcare professional assessment scale individually scores the extent and severity of erythema, dry desquamation, moist desquamation, and necrosis using a 5-point scale from 0 to 4. Erythema is rated based on the degree of color change. Dry desquamation, moist desquamation, and necrosis are rated based on the percentage of the treatment area affected by that particular reaction. The patient component focuses on skin tenderness, itching, burning, and functional activity using a 4-point scale from 1 to 4. The Healthcare Professional Assessment Scale scores and the Patient Symptom Scale scores are added together for a total skin reaction score. The higher the score, the worse the skin reaction. The Healthcare Professional Assessment Scale will be completed by the radiation oncologist in person at Mid-Study Visit, EndRT Visit, and 2-Week Post-RT Visit. The Patient Symptom Scale will be completed by the subject at the Mid-Study Visit, EndRT Visit, and 2-Week Post-RT Visit. Study personnel will enter the data from the completed forms into REDCap.

HEALTHCARE PROFESSIONAL ASSESSMENT SCALE

	0	**1**	**2**	**3**	**4**
Erythema (E)	Normal Skin	Dusky pink	Dull red	Brilliant red	Deep red/purple
Dry Desquamation (DD)	Normal Skin	<25%	>25-50%	>50-75%	>75-100%
Moist Desquamation (MD)	Normal Skin	<25%	>25-50%	>50-75%	>75-100%
Necrosis (N)	Normal Skin	<25%	>25-50%	>50-75%	>75-100%

PATIENT SYMPTOM SCALE

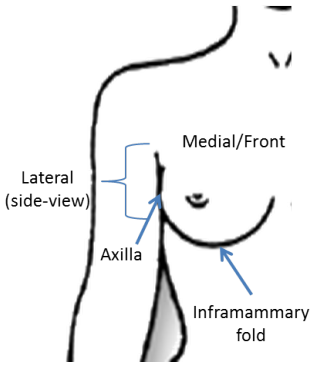
	Not at all	**A little**	**Quite a bit**	**Very much**
Tenderness, Discomfort, or Pain?	1	2	3	4
Itch?	1	2	3	4
Burning sensation?	1	2	3	4
Skin reaction interfered with day to day activities?	1	2	3	4

Dermatology Life Quality Index (DLQI): This is a self-report 10-item questionnaire that measures how much a skin problem (i.e., radiation dermatitis) has affected the subject's quality of life (24, 25, 26). Subjects will be asked 10 questions about how their skin problem has affected different aspects of their life over the last week. Subjects will respond on a 4-point scale: 0 = Not at all; 1 = A little; 2 = A lot; and 3 = Very much. Subjects can also state whether a question is "not relevant," which will be scored as 0. The DLQI is scored by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. Scores will be interpreted for overall effect on subject's quality of life: 0-1 = no effect; 2-5 = small effect; 6-10 = moderate effect; 11-20 = very large effect; 21-30 = extremely large effect. This questionnaire will be completed by subjects on paper during each study visit:

- Baseline Visit
- Mid-Study Visit
- EndRT Visit
- 2-Week Post-RT Visit

Digital Photographs of Skin: Digital photographs (i.e., images) will be taken of the irradiated skin of the whole breast to which Silverlon® dressing was applied. Images of three different locations (medial/front breast, lateral breast, and inframammary fold,) will be captured within the RT site during the Baseline Visit, Mid-Study Visit, EndRT Visit, and 2-Week Post-RT Visit (Figure 2). The Baseline Visit photographs will be to image the skin prior to application of Silverlon® dressing. Digital photographs will be taken of areas where Silverlon® dressings were applied within the radiation treatment area. The photographs should document the severity of radiation dermatitis and be representative of the RTOG score given to a subject for that specific time point. Do not exceed 4 photographs for each time point for each subject (i.e., Baseline Visit, Mid-Study Visit, EndRT Visit, and at 2-Week Post-RT Visit per subject). These digital photographs will only be used for this study and will not be included in subject's medical record. The digital photographs will be de-identified (i.e., only labeled with Study ID and assessment week). During the study, the digital photographs will be stored on a password-protected, desktop computer in a locked office by Dr. Ryan Wolf. Upon completion of the study, the digital photographs will be stored at the University of Rochester.

Figure 2: Four location within the breast radiation area



Digital images will be taken with an Apple 7th Generation iPad camera. The iPads will be used for data collection and locked down for utilization of REDCap and University's Box app. The digital images will be stored directly into Box, which is password-protected, secure on the University network, and HIPAA compliant. Study personnel will take a "close-up" image of the skin that is in focus. Study personnel will avoid shadowing of the skin in the images. The photographs will be taken at these time points:

- Baseline Visit
- Mid-Study Visit
- EndRT Visit
- 2-Week Post-RT Visit

Withdrawal Form: This electronic REDCap form will be used to document the time and reasons for withdrawals during the study. The data from this form will be electronically entered into the secure REDCap database at the University of Rochester Medical Center.

Comprehensive Study Log: This is a password-protected excel spreadsheet that contains a log for all subjects in the study. The information kept in this file include: Subject ID, Subject Name, Subject MRN, Screened & Eligible, Consent Completed, Screen Fail, Size Silverlon® dispensed, Baseline Complete, Weekly Phone Calls Completed, Mid-Study Visit Complete, EndRT Visit, 2-Week Post-RT Visit Completed, Completed Study, Withdrawn, and Loss to Follow-up. Study personnel will complete the required subject information (i.e., dates, etc.) and check the appropriate boxes (i.e., completed = green fill; incomplete = red fill) as the study progresses to monitor subject participation in the study.

EndRT Data Form: This is an electronic REDCap form for the collection of final radiation therapy information for each subject. The information on the form includes: RT Type (conventional vs. short-course), positioning (prone vs. supine), total radiation dose, fractionation, breast field separation (cm), boost dose (if any), bolus (if used), and any delays in RT. Study personnel will enter the data electronically into the secure REDCap database at the University of Rochester Medical Center.

Silverlon® Compliance Log: This is a paper form on which the subject will document each time they remove the Silverlon® dressing and apply the Silverlon® dressing. The subject will also indicate the reason for removal of Silverlon® dressing (i.e., radiation treatment session, bathing/showering, swimming, or other. If the subject selects "other" for removal, the subject should describe the reason in the space provided). This is a paper form that the subject will take home with them and complete as necessary daily whenever the Silverlon® dressing is removed and put back on. The subject will be given a new Compliance Log every 7 days with the two new Silverlon® Dressings. The subject will return their completed log to study personnel every 7 days.

Silverlon® Accountability Record: This is a paper form that will be kept with the provided Silverlon® dressings in Radiation Oncology at University of Rochester. This form will record: the size and number of the dressings in stock, the dispense date of any dressings, Subject ID for dispensed dressings, initials of study personnel, number of dressings dispensed, and adjusted number of dressings in stock. This form will be completed each time Silverlon® dressings are dispensed to a study subject.

90-Day Phone Call Form: This is an electronic REDCap form collects the answers to the questions asked during the 90-Day Follow-Up that will occur 90 days after the start of RT. Study personnel will ask the subject: 1) Since your 2-Week Post-RT visit, has your skin reaction in the area where the Silverlon® dressing was applied improved, stayed the same, or worsened?; 2) Do you have any skin pain in the area where the Silverlon® dressing was applied? (yes/no); 3) Do you have any itching in the area where the Silverlon® dressing was applied? (yes/no); 4) Do you feel like your skin in the radiation treatment area has fully recovered? (yes/no); and 5) Would you recommend Silverlon® dressing to other patients during radiation therapy? (yes/no). For question 1, if the subject answers "worsened", study personnel will document the description of

the skin reaction in the provided area on the form and will notify the treating radiation oncologist.

5.4. SUBJECT COMPLIANCE

Compliance will be measured using a patient-reported compliance log, **Silverlon® Compliance Log**. Subjects will be asked to complete a **Silverlon® Compliance Log** to document the removal and application of the Silverlon® dressing during the course of the study. They will enter the date and time of removal and application of the Silverlon® dressing every time these actions occur. This will provide insight into how many hours per day the Silverlon® dressing was worn on the irradiated breast. Additionally, study personnel will ask the subject if they have been "wearing the Silverlon® while sleeping" each week by phone and at each study visit.

5.5. COST TO SUBJECTS

There are no costs for participation for research subjects in this study. Silverlon® dressings will be provided to the subjects at no cost. There is no additional travel above the usual travel required for the course of radiation therapy associated with this study.

5.6. REIMBURSEMENT FOR PARTICIPATION

All subjects will be reimbursed $200.00 for completion of all study procedures in this study. Payment will be prorated based on the number of study visits completed in the study. Subjects will be paid $20 for completion of baseline visit (Pre-Radiation visit), $60 for completion of Mid-Study Visit, $60 for completion of Completion of RT Visit, and $60 for completion of 2-Week Post-RT Visit. A check or VISA Gift Card will be issued and mailed to the subject after completion of the 2-Week Post-RT Visit or at their completion of study participation.

6. CONCOMITANT AND DISALLOWED MEDICATIONS

This is a safety study for Silverlon® dressing to discern FDA indication for radiation dermatitis. For this reason, current standard of care for radiation dermatitis will not be allowed during the study. Topical agents usually provided to patients during radiation therapy, such as RadiaPlex, Aquaphor, or other moisturizing lotions are not permitted during the study. The goal of the study is to determine if Silverlon® dressing is safe to use during radiation therapy and can be used in place of other current topical agents. Oral antihistamines are permitted to help with itching or other symptoms. Standard of care for radiation dermatitis is only permitted if the subject is withdrawn from the study due to the progression of the skin reaction to RTOG score ≥3 (i.e., moist desquamation in areas that are not skin folds). If the subject is withdrawn for this reason, then standard of care (i.e., silver sulfadiazine, topical steroids, Mepilex, etc.) are permitted.

6.1 USE OF TOPICAL AGENTS FOR WORSENING SKIN REACTIONS

In an effort to prevent moist desquamation and reduce patient withdrawal from study, use of standard of care topical medications may be allowed only under the following circumstances:

- Subject should have documented worsening skin reaction that requires additional treatment per the treating physician, and be ordered/prescribed the topical agent by the

treating provider on study.

- The type, dose and frequency of the medication prescribed will be documented in the subject's study and medical record.
- The subject will be instructed to remove the Silverlon® dressing before applying the topical agent, and reapply the dressing approximately one (1) hour after application of the topical agent to allow for absorption into the skin. The subject will be asked to document the removal and re-application of the dressing in their Subject Compliance Log.

7. SUBJECT WITHDRAWALS

Subjects will be advised during the consent process that they have the right to withdraw from the study at any time without prejudice or reason. Subjects that withdraw from the study will be replaced with another subject. Subjects will continue to receive radiation therapy as prescribed with standard of care with their treating radiation oncologist. The reason for discontinuation will be recorded in the subject's medical records. The date of occurrence and reasons for any subject withdrawal will be recorded and documented on the **Withdrawal Form**.

Subjects can be withdrawn from the study by the investigator or radiation oncologist for: non-compliance to study procedures; termination of funding; allergic reaction to Silverlon® dressing; worsening of the disease under study; intercurrent illness; pregnancy; or progression of skin reaction to RTOG score ≥3 in the radiation area where the Silverlon® dressing has been applied (i.e., whole breast). RTOG score ≥3 requires patients to have areas moist desquamation outside of skin fold regions (i.e., which would exclude inframammary fold and axillas because these are skin fold regions). Additionally, an area of moist desquamation that is >50% of the radiation treatment area (i.e., RISRAS-HPA score ≥3). Therefore, a large area of moist desquamation outside of skin folds would suggest withdrawal. Pinpoint areas and fold areas of moist desquamation could not require withdrawal. Patients withdrawn from the study will stop using Silverlon® dressing, but continue to receive radiation therapy on their normal schedule as prescribed by the treating radiation oncologist. For patients withdrawn from the study, standard of care for radiation dermatitis will be provided by the treating radiation oncologist, who will continue to follow the patient as per their normal clinical routine. The date of occurrence and reasons for any subject withdrawal will be recorded and documented on the **Withdrawal Form**. An adverse event will be reported if the skin reaction is RTOG ≥4. This grade of radiation dermatitis is severe and should be reported on the AE Source Doc and following reporting procedures stated in §10. Allergic reaction to Silverlon® dressing will be reported as an unexpected side effect on the AE Source Doc.

8. EARLY STOPPING PROCEDURES

The study will be stopped if we observe a significantly increased rate of confluent moist desquamation (i.e., RTOG ≥3; large areas (>50% of radiation treatment area) of moist desquamation outside of skin folds) in subjects using the Silverlon® dressing. The study will be stopped if 6/15 or fewer subjects who initiated treatment with Silverlon® dressing are withdrawn due to RTOG score ≥3. This result would suggest a two-fold increase in the rate of confluent moist desquamation with patients using Silverlon® dressing. If the first 6 subjects are withdrawn due to RTOG score ≥3 while using the dressing (i.e., 6/6), the study will be stopped due to the significantly increased rate of confluent moist desquamation. If the study is stopped early, participant reimbursement will be issued to any subjects remaining on study.

9. RISK/BENEFIT ASSESSMENT

9.1. POTENTIAL RISKS

The proposed study is a low risk safety clinical trial. The only patient intervention in this study is the application of Silverlon® dressings to the radiation site. No adverse reactions or events have been reported for Silverlon® dressings. Subjects may find the dressing uncomfortable to wear inside the bra. However, discomfort while wearing has not been reported. Unexpected side effects, such as allergic reactions, may occur and are unpredictable. This reaction may be mild, such as a skin rash, or you may have more severe symptoms like swelling of the throat, low blood pressure, and shortness of breath. If any of these unexpected side effects occur, subjects will be advised to stop use of their intervention immediately. Subjects will be informed about any additional potential risks if they are discovered. Furthermore, while we make every effort to keep all data and study information private, this cannot be guaranteed. All data will be de-identified and stored in a locked file in a locked office. All appropriate procedures will be taken to maintain subject privacy and data collected during this study.

9.2. PROTECTION AGAINST RISKS

The study protocol, amendments to the protocol, consent forms, study forms and patient-report forms are reviewed by the responsible IRB, University Research Subjects Review Board (RSRB), prior to implementation. The RSRB also provides continuing review of study conduct and consent.

The research staff (*PI, Co-investigators, study coordinator)* will conduct continuous review of data and subject safety. The review will include the number of subjects, adverse reactions, and responses observed. The Investigator will submit summaries of this data to the Research Subjects Review Board (RSRB) for review as required in the study's protocol review committee approval letter.

Study forms and patient-report forms are either electronic forms through REDCap, excel spreadsheets, or paper forms. All data from paper forms will be entered electronically into REDCap database as it is received from the subjects. All electronically captured data will be securely stored in the secure REDCap database at the University of Rochester Medical Center. To protect the confidentiality of subjects, questionnaires and data collected on each subject will be coded, the form collected will contain a numerical Subject ID and Subject Initials. The forms contain the minimum personal identifiers needed for research. The key list with all Subject IDs will be kept in a locked file. All forms will also be kept in a locked file that is separate from the key list that links the subject name and the code number. When data analyses are completed, the key list and paper forms will be destroyed. The required informed consent will be the only record kept of those subjects who have participated in the research. The Silverlon® dressing that will be studied in this project is not associated with any risks.

Any safety information for an individual patient that is volunteered by a study participant during the course of this research will be documented. All adverse events, whether observed by the Investigator, radiation oncologist, or nurse, elicited from or volunteered by the subject, will be documented and reported as described in §10. Each adverse event will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, contributing factors, and any actions taken. This description will be in the summary not during a subject's regularly scheduled clinic appointment.

9.3. POTENTIAL BENEFITS TO THE SUBJECTS

It is not possible to predict whether subjects will feel any personal benefit from participation in this research study. Subjects may have relief of radiation dermatitis and associated pain and itching, as well as improved quality of life. The study will provide insight into the safety and use of Silverlon® dressing for radiation dermatitis. Subjects will receive reimbursement for their participation in this study (See §5.6).

9.4. ALTERNATIVES TO PARTICIPATION

Subjects who do not participate in this study will receive the current standard of care for radiation dermatitis at the University of Rochester Medical Center. Study participation is voluntary. Subjects can choose to not to take part or withdraw from the study at any time, for whatever reason.

10. SAFETY AND REPORTABLE EVENTS

10.1. ADVERSE EVENT MONITORING

This study does not involve interventional or clinical endpoints for individual patients. This is a safety study to determine if Silverlon® dressing can be indicated for radiation dermatitis. The primary outcome is not clinical response to treatment; it is safety (i.e., adverse reactions/events/complications). Any adverse event will be documented on the AE Source Doc throughout the course of the study. Any safety information for an individual patient that is volunteered by a study subject during the course of this research must be reported as described below:

All adverse events, whether observed by the Investigator radiation oncologist, or nurse, elicited from, or volunteered by the subject, will be documented. Each adverse event will be recorded on the electronic AE Source Doc. This form will record the will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, contributing factors, and any actions taken. This description will be in the summary not during a subject's regularly scheduled clinic appointment.

Adverse event (AE): is any untoward medical occurrence in a subject using study device, and which does not necessarily have a causal relationship with this treatment. An adverse event can be any unfavorable and unintended sign (including abnormal laboratory test results), symptom, or disease temporally associated with the use of the study device, whether or not considered related to the study device. The relationship of each adverse event to the study device must be recorded as one of the choices on the scale described below.

Attribution: An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to treatment.
Unlikely	The AE is *doubtfully related* to treatment.
Possible	The AE *may be related* to treatment.
Probable	The AE is *likely related* to treatment.
Definite	The AE is *clearly related* to treatment

Hospitalization (or prolongation of hospitalization): For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
Life Threatening Adverse Event: Any AE that places the subject at immediate risk of death from the AE as it occurred.

Serious Adverse Event (SAE): Any adverse event occurring at any dose that results in **ANY** of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious when, based upon medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2. RECORDING ADVERSE EVENTS

Study personnel will assess adverse events by recording all voluntary complaints of the subject. Any side effects and adverse reactions will be noted on the AE Source Doc. Study personnel will check with the nurse and/or treating radiation oncologist regarding any reported adverse reactions. All adverse events, whether observed by the Investigator, the treating radiation oncologist, or volunteered by the subject, will be documented. Adverse events will be reported per the University of Rochester Research Subjects Review Board (RSRB) reporting requirements. Each adverse event will include a brief description of the experience, the date of onset, the severity of the event, the relationship to investigational intervention, and any action taken with respect to the study and intervention. Adverse event monitoring will occur at the start of informed consent until completion of the study.

The relationship to the study device and the severity of each adverse event (i.e., attribution) as judged by the investigator or radiation oncologist must also be recorded. An adverse event is any untoward medical occurrence in a subject administered study device, and which does not necessarily have a causal relationship with this treatment. The relationship of each adverse event to the study device must be recorded as one of the choices on the scale below:

DEFINITE: Causal relationship is certain (e.g., the temporal relationship between device use and the adverse event onset/course is reasonable; there is a clinically compatible response to de-challenge; other causes have been eliminated; and the event must be definitive pharmacologically or phenomenologically using a satisfactory re-challenge procedure, if necessary).

PROBABLE: High degree of certainty for causal relationship (e.g., the temporal relationship between device use and the adverse event onset/course is reasonable; there is a clinically compatible response to de-challenge [re-challenge is not required]; and other causes have been eliminated or are unlikely).

POSSIBLE: Causal relationship is uncertain (e.g., the temporal relationship between device use and the adverse event onset/course is reasonable or unknown; de-challenge/re-challenge information is either unknown or equivocal; and while other potential causes may or may not exist, a causal relationship to study device does not appear probable).

UNLIKELY: Not reasonably related, although a causal relationship cannot be ruled out (e.g., while the temporal relationship between device use and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study device).

UNRELATED: No possible relationship (e.g., the temporal relationship between device use and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to the device is not plausible).

10.3. REPORTING SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs), while a subject is enrolled in the study until the subject completes the study, will be reported in writing to the University RSRB as per their requirements. A serious event refers to any event in which the outcome results in any of the following: death, a life-threatening adverse device experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability, incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study, will not be considered serious adverse events. The onset date, resolution date, treatment, and outcome of each adverse event will be reported to the Research Subjects Review Board (RSRB) and to the Safety Coordinator using the MedWatch Form FDA 3500A-Mandatory Reporting. Unanticipated problems that involve risks to subjects or others (UPIRTSO) will be reported to the University RSRB and Sponsor.

IRB: As described above, on-study adverse reactions are reported to the University of Rochester Research Subjects Review Board (RSRB). Modifications to the protocol will be reviewed by RSRB before implementation. The RSRB also provides initial and continuing review of study conduct and consent.

Research staff (i.e., PI, Co-investigators, or study coordinator): Will also conduct continuous review of data and subject safety. The review will include for each treatment arm/dose level: the number of subjects, adverse reactions, and responses observed. The Investigator will submit summaries of this data to the Data Safety Monitoring Committee for review as required in the study's protocol review committee approval letter.

11. DATA AND SAFETY MONITORING PLAN

Dr. Sughosh Dhakal (co-investigator) in Radiation Oncology at University of Rochester will serve as the Clinical Monitor for this study. Approval of protocol, informed consent

procedures, and recruitment will be obtained from the University RSRB. Any safety concerns about the clinical protocol will be brought to the immediate attention of the Principal Investigator and Co-investigator. Study personnel will follow aforementioned reporting procedures for adverse event reporting, including any serious adverse events. Protocol deviations and quality issues will be recorded and reported to the IRB per local policies. Remedial and/or corrective action to prevent reoccurrence of protocol deviations or quality issues will be instituted as necessary. Because this study's procedures pose relatively low risk to subjects, monthly data and procedural reviews by the Clinical Monitor and Investigator in consultation with study personnel will be sufficient to identify and ameliorate any potential safety issues. As such, an additional Data and Safety Monitoring Plan document will be not be created for this study.

Patients will have their radiated sites examined once a week by either a radiation oncologist as part of their regular course of radiation therapy. At this examination, any adverse events related to their skin will be recorded. For the purpose of this study, an adverse event will be defined as severe radiation dermatitis meeting the definition of RTOG score grade 4 or above (ulceration, hemorrhage or necrosis) or other adverse reaction of Grade 3 or higher in the area of radiation area where Silverlon® dressing is applied. Patients meeting the definition of 'adverse event' will be withdrawn from the study and the radiation dermatitis then treated according to local protocol as ordered by the attending radiation oncologist. Changes in dose or scheduling of radiation therapy in response to an adverse event will remain the responsibility of the attending radiation oncologist.

If a patient feels that they are having an adverse event outside of the weekly monitoring schedule, they may contact the study coordinator or principal investigator by phone and an immediate follow-up appointment with the radiation oncologist will be arranged.

12. STUDY MONITORING PLAN – Sponsor

The Sponsor and/or designee will monitor the study over its duration. The Sponsor study monitor, Clinical Research Associate (CRA) will visit the site at appropriate intervals to review investigational data for accuracy and completeness and ensure compliance with the protocol. Medical records/source documents (office, clinic or hospital) will be reviewed for subjects looking for primary end-point events. In cases of all-cause mortality and SAE, the study monitor will perform inspection for pertinent documents and records for these events. The CRA will be assisting the site to resolve any data queries and ensuring that relevant source documents related to study events are being retrieved from the site. The Investigator/site will permit access to such records. Source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and study device information. A monitoring visit sign-in log will be maintained at the site. The Investigator, Clinical Monitor, and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the study monitor with a suitable working environment for review of study-related documents.

13. DATA ANALYSIS AND MONITORING

13.1. Sample Size Justification

The study will recruit 36 total subjects to accrue 30 fully evaluable subjects with an estimated 20% withdrawal rate. The target enrollment table in §3.9 shows that we have access to enough eligible patients to complete this study in 12 months. The following table shows the

precision estimates and 95% confidence intervals for our primary objective (i.e., adverse events related to Silverlon®) and secondary objective (i.e., compliance and withdrawal rate). Our estimates for adverse events (primary and intent to treat analyses) are based on published trials showing no reported adverse events or allergic reactions to silver nylon dressing in patients receiving radiation (8, 15-17). Our estimates for the primary objective were conducted with sample size of 30 for the fully evaluable subjects and 36 for all subjects that initiated treatment. Our estimates for compliance (secondary analyses) are based on the Aquinos-Parsons *et al* study in breast cancer patients that showed a 97% compliance rate for silver nylon dressing (8). Our estimates for compliance were conducted using sample size of 30 for fully evaluable subjects. In subjects that withdraw from the study, we will be able to partially evaluate compliance because of their early termination of treatment and study procedures. Our estimates for withdrawal are based on the Vavassis *et al* study in head & neck cancer patients using silver nylon dressing that reported 1 of 12 subjects (i.e., 8%) withdrew from the study (17). Our estimates for withdrawal were conducted using a sample size of 36 to capture all subjects that initiated treatment. 95% Exact Clopper Pearson confidence intervals on the expected proportion have been generated using SAS 9.4.

95% Confidence Intervals						
Objective	**Measure**	**Sample Size**	**Proportion Estimate**	**Expected Observed Count**	**95% LCL**	**95% UCL**
Primary	# Adverse Events per number of patients	30	0	0	0	0.116
Intent to Treat	# Adverse Events per number of patients	36	0	0	0	0.097
Secondary	Compliance	30	0.97	29	0.828	0.999
Secondary	Withdrawal	36	0.166	6	0.064	0.328

13.2. Statistical Analyses

This is a safety study to determine Silverlon® dressing indication for radiation dermatitis. Descriptive statistics will be used to describe the study subject population. The primary analyses will evaluate the number of adverse events or reactions reported (if any) at the breast irradiation site where the Silverlon® dressing was applied. The primary analyses will be conducted on 30 fully evaluable subjects (i.e., 30 subjects that fully complete the study) and on all subjects that initiated treatment with Silverlon® dressing in an intent to treat analysis (see section 13.1). For a safety study, it is important to obtain the overall adverse event rate for all subjects that initiated treatment and all subjects who fully completed the study.

The secondary analyses will evaluate the compliance rates for the Silverlon® Dressing during RT and post RT. Compliance will be on the number of days during RT and post-RT that the dressing was worn. We expect compliance rate to be 97% (8). Additionally, we will evaluate the percentage of subjects that removed the dressing for sleeping. Subjects are asked to wear the dressing during sleep and only remove the dressing for RT sessions, showering/bathing, or swimming. Furthermore, we will calculate the number of hours during a day that the dressing was not worn summing the time between removal and application of the dressing each day.

Compliance will be evaluated in the 30 fully evaluable subjects. Although we can and will evaluate compliance in all subjects that initiated treatment, these analyses will not provide a complete picture of compliance due to early termination of study procedures. Furthermore, the secondary analyses will also evaluate withdrawal rates due to the Silverlon® dressing in all subjects who initiated treatment. We expect less than 6 subjects to withdraw due to the Silverlon® dressing. The exploratory analyses will assess trends in radiation dermatitis severity (i.e., RTOG and RISRAS) and quality of life (DLQI) during the course of the study. These analyses will also be able to evaluate changes in skin symptoms experience by the patient based on the RISRAS-Patient Symptom Scale during RT.

14. DATA HANDLING, CONFIDENTIALITY, AND STORAGE

All research data are specifically used for only research purposes and will contain the minimum personal identifiers required for the research. All written materials will be kept confidential, locked in the private office of the research coordinator and identified only by Subject Pair IDs (i.e., numbers) and initials. All data will be stored in a locked office in a locked cabinet and/or on a password-protected computer in a locked office. Results of the research may be presented at meetings or published for scientific purposes, but subject identification information will not be used. All of the forms listed below will be used in this study:

- Eligibility Checklist (paper)
- Screening Log (REDCap)
- Study Reimbursement Form (paper)
- W9 Form (paper)
- Withdrawal Form (REDCap)
- Comprehensive Study Log (password-protected Excel spreadsheet)
- OnStudy Data Form (REDCap)
- Silverlon® Compliance Log (paper)
- RTOG Scale (REDCap)
- RISRAS-Healthcare Professional Assessment Scale (REDCap)
- RISRAS-Patient Symptom Scale (REDCap)
- Dermatology Life Quality Index (DLQI) (REDCap)
- EndRT Data Form (REDCap)
- Weekly AE/Chart Review Source Doc (REDCap)
- Questions Log (REDCap)
- 90-Day Phone Call Form (REDCap)
- Drug (Silverlon) Accountability Record (paper)

The majority of forms will be completed electronically. The Comprehensive Study Log are password-protected excel files only accessible by study personnel and will be stored in the study folder on the secure Dermatology CTU's sharedrive (i.e., smd drive). All other study forms will be electronic forms completed using REDCap. The patient and caregiver PROs will be completed via iPad and electronically stored in REDCap. All forms will be available in pdf format for completion on paper in case there are any issues with the electronic forms. Forms completed on paper will be kept confidential, locked in the private office of the research coordinator or the study PI.

Data Monitoring: The REDCap database will be audited monthly to ensure accurate data collection and entry. The PI will meet with study personnel weekly to discuss study accrual, study procedures, and data collection. No subject identifying data will be used. All of the written material will be kept confidential, locked in the private office of the principal investigator and identified only by Subject ID. At completion of the whole study (including final analyses), all

paper forms will be destroyed.

Data Storage and Confidentiality: All measures completed on the iPad will be electronically stored in REDCap database at the University of Rochester Clinical & Translation Science Institute's (CTSI) secure REDCap data server, accessible only by Dr. Ryan Wolf and assigned study personnel using their University-specific login and password. All completed paper questionnaires will be stored in study folders in a locked cabinet in Dermatology CTU or Dr. Ryan Wolf's office private locked office. All paper questionnaire data will be electronically entered into the REDCap database using an electronic data collection form. All forms will be coded by Subject Pair ID and Initials. The coding key will be stored electronically on the password-protected, encrypted, desktop computer connected to the University's secure server in Dr. Julie Ryan Wolf's office. The coding key will be stored for the length of the study and then permanently deleted at the completion of the study.

All data for this study is electronic and will be stored in the secure, study-specific, password-protected REDCap database or on the secure Dermatology CTU's University sharedrive. All paper documents will be stored in a locked file cabinet in Dermatology CTU or Dr. Ryan Wolf's the principal private office in the Department of Dermatology. Study personnel will have access to the study data. Statistical analyses will be performed on de-identified dataset containing Subject Pair IDs.

Study data, compliant with all HIPPA regulations, will be provided to the Sponsor (Argentum Medical) and BARDA teams assigned to this project. This will include individual and composite/analyzed data. All data will be electronic and can be shared with Argentum through encrypted email or other secure file sharing method (Box, Dropbox, etc.). Study data will be shared within the Argentum Research Team, and with the BARDA team assigned to this project. Composite data will be submitted to the FDA in support of a 510(k) application for additional indication of radiation dermatitis. FDA has the right to request access to the base or individual data.

All electronic and paper records and analysis will be retained for a period of 2 years following the date a marketing application is approved for the device (i.e., dressing) for the indication for which it is being investigated. If no marketing application is filed or if the application is not approved for such indication, data and records will be retained for a period of 2 years after the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application. After the specified retention period, paper forms will be destroyed and the electronic records will be permanently deleted.

It is anticipated that the principal investigator, the Argentum research team, or both will publish results of this study in the peer-review literature. Protection of patient confidentiality will follow all standard rules in place for publication in the medical literature.

15. SCHEDULE OF EVENTS AND DATA COLLECTION

Study Procedures	Screening	Baseline[2]	Weekly During RT	Mid-Study RT	EndRT	2-Week Post-RT	90-Day Phone Call[6]
Eligibility Checklist[1]	X						
Informed Consent[1]	X						
Reimbursement Form/W9		X					
OnStudy Data Form Log		X					
Silverlon® Accountability Record		Completed as needed throughout the study					
Digital Photographs of Skin		X		X	X	X	
Radiation Oncologist:							
RTOG				X	X	X	
RISRAS-HPAS				X	X	X	
Patient PROs:							
Silverlon® Compliance Log[5]		X	X	X	X	X	
DLQI		X		X	X	X	
RISRAS-PSS				X	X	X	
Screening Log[3]		Completed as needed throughout the study					
Comprehensive Study Log[4]		Completed as needed throughout the study					
Weekly AE/Chart Review Source Doc			X	X	X	X	
Questions Log			X	X	X	X	
EndRT Data Form					X		
90-Day Phone Call Form							X
Withdrawal Form		Completed as needed throughout the study					

[1]Eligiblity Checklist and Informed Consent can be completed at same visit as the Baseline visit.
[2]Baseline Visit can be performed at the same visit after informed consent is obtained. Baseline visit must be performed before the first day of radiation therapy.
[3]Screening Log will be completed to keep track of subjects that are approached about the study and decline or agree to participate in the study.
[4]The Comprehensive Study Log will keep track of subject's status during the study until study completion.
[5]A new Silverlon® Compliance Log will be given to the subjects every 7 days when new Silverlon® dressings are dispensed. The completed Silverlon® Compliance Log will be collected at this time.
[6]The 90-Day Phone call was requested by FDA to monitor subjects up to 90 days. The call will occur at 90 days after the start of radiation therapy. It is expected that any acute radiation-induced skin reactions will have recovered by this time.

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Appendix A. 90-DAY FOLLOW UP FOR MYCHART

The following message will be sent to subjects through MyChart in order to complete the 90-Day Follow Up portion of the study.

Message Subject: Silverlon 90-Day Follow Up Questions

Message Body:

Dear [INSERT SUBJECT NAME],

Please answer the 90-Day Follow-Up questions below:

1. Since your 2-Week Post-RT visit, has your skin reaction in the area where the Silverlon® dressing was applied **improved**, **stayed the same**, or **worsened**?

   If **worsened**, please describe:

Please answer the following questions with either "yes" or "no":

2. Do you have any skin pain in the area where the Silverlon® dressing was applied?
3. Do you have any itching in the area where the Silverlon® dressing was applied?
4. Do you feel like your skin in the radiation treatment area has fully recovered?
5. Would you recommend Silverlon® dressing to other patients during radiation therapy?

Thank you,

[INSERT COORDINATOR NAME]