**Appendix A. Protocol**

**Mepitel Film vs StrataXRT Gel in managing radiation-induced skin reactions in chest wall patients**

**Background**

Breast cancer is the most common malignancy for women in New Zealand. Radiation-induced skin reactions occur in 80-90% of breast cancer patients by completion of treatment [1] and can severely affect patient comfort levels and poses a risk of infection in these patients who, due to their conditions and treatment, may be immuno-compromised. In extreme cases extensive moist desquamation (MD) may result in a treatment break, which may compromise local control and patient outcomes. Skin care practices vary between institutions worldwide with considerable intra-institution variability, and is mainly based on historical and anecdotal evidence.

In the last decade our group has completed five trials in New Zealand that compared the effect of soft silicone dressings with that of standard care on the severity of acute radiation-induced skin reactions in breast cancer [2–4] and head and neck cancer patients [5,6]. All trials were intra-patient randomized controlled trials (RCT), whereby each patient acted as their own control, circumventing the problem of the many confounding treatment-and patient-related factors that affect the severity of such skin reactions.

We observed a decrease in skin reaction severity in all of the trials in skin covered by soft silicone dressings. In every instance this was a statistically significant decrease at the 5% level. We concluded therefore that soft silicone dressings do have a beneficial effect on skin reaction severity in the study population. The effect observed was most pronounced in breast cancer patients (who received a lower dose than head and neck cancer patients) and in a prophylactic setting where dressings are applied from day 1 of radiation therapy.

The soft silicone dressings we have used in our trials are coated with a soft silicone adhesive layer based on the patented *Safetac* technology. The dressings adhere to healthy skin but do not cause trauma on removal. The material does not react with chemicals in or on the skin, does not stick to open wounds and can be left on the skin for at least a week. Soft silicone dressings reduce skin reactions by creating a moist healing environment and preventing friction between damaged skin and clothing or other body parts of the skin that has been sub-lethally damaged by radiation. This allows for repair of the fragile skin rather than exacerbating the damage.

**Motivation for doing this trial**

Mepitel Film (from here on referred to as Film) has been the most successful of the silicone dressings as it is transparent and can be kept on during radiation. This has allowed us to run prophylactic trials, where the Film is applied on the first day of radiation therapy. In this way, the skin is protected from friction from the start of radiation therapy and the prophylactic trials have shown a much greater effect on skin reaction severity than management trials, where the Film is applied after erythema is evident.

One of the negative aspects of Film is that it needs to be applied very carefully by a radiation therapist or an oncology nurse with the patient in the treatment position. It is important that the shape of the breast is not altered in any way and that the pieces of Film are not stretched or overlapped with other pieces of Film. The Film is replaced every week or more often in some patients, which takes up valuable staff resources.

StrataXRT Gel (from here on referred to as Gel) is a silicone gel product that forms a thin silicone film when rubbed onto the skin, presumably with similar protective properties [7]. Gel is applied by the patients themselves twice a day, requiring fewer hospital resources.

We intend to conduct a RCT to compare the protective effects of Film and Gel on the skin of breast cancer patients who undergo radiation therapy after mastectomy.

**Hypotheses**

H0: the number of skin patches that develop MD under the Gel is greater than under the Film plus 7.5%

HA: the number of skin patches that develop MD under the Gel is smaller or equal than under the Film plus 7.5%

**Aims and objectives**

**Primary aim**

To determine the incidenceof moist desquamation in skin covered by Film and skin covered by Gel during and immediately after radiation therapy of the chest wall.

**Secondary aims**

1. To compare overall skin reaction severity of skin underneath both interventions using both researcher and patient reported outcomes
2. To compare patient satisfaction with both interventions
3. To compare the costs associated with using each intervention

**Primary outcome**

Measure the incidence of moist desquamation in skin patches covered in Film and Gel using the researcher component of RISRAS and the expanded RTOG

**Secondary outcomes**

1. Measure the overall skin reaction severity in skin patches covered in each of the interventions using both the researcher and patient components of RISRAS and expanded RTOG
2. To measure patient satisfaction with both interventions using an exit questionnaire
3. To do an in-depth cost analysis in the costs involved in using each intervention, both with respect to the direct cost of the product per patient and the indirect cost of radiation therapist/nursing time per patient

**Study design**

**This is a multicentre open label intra-patient-controlled randomised clinical trial with partial blinding.**

The trial will be run in a number of NZ hospitals. This will be an open label trial because the participants and radiation therapists/oncology nurses can see where the Film and Gel are on the chest wall. We will have an independent researcher familiar with the scoring systems, score both sides of the chest wall in the second week after completion of treatment to provide an unblinded score.

**Participants**

***Participant inclusion criteria***

All women aged 18 years and over receiving radiation for breast cancer after having had a mastectomy.

***Participant exclusion criteria***

* Distant metastatic disease
* Previous radiation to chest area
* Skin conditions that may aggravate RT-induced reactions
* Karnofsky score <70
* Not able to come to 4 follow up sessions

***Participants act as their own controls***

Using intra-patient controls circumvents confounding patient-related and treatment-related factors. Randomization will circumvent the effect of potential small dose differences between the areas with Film and the areas with Gel. The chest area that is to be irradiated will be divided into a lateral and medial half at the start of radiation therapy treatment. Each half will be randomized to either Film or Gel.

**Description of Radiation Therapy Treatment**

Radiation should be given as 26Gy in 5 fractions (1 week), 40Gy in 15 fractions (3 weeks) or 50Gy in 25 fractions (5 weeks) or another biologically equivalent dose and per institution’s normal practice at the treating clinician’s discretion. There are several regimens in common use but intra-patient comparison negates this variable. Information on planning techniques, dose, bolus procedures, chemotherapy or hormone therapy will be recorded as below:

* ***Treatment-related*:** RT delivery method (3dCRT, IMRT, Intensity Modulated Arc Therapy), RT regime, boosts, chemo regime, surgery
* ***Cancer-related:* Type of cancer,** Location of primary tumour, TNM Stage
* ***Patient-related:*** Ethnicity, Age, Weight, BMI, Smoking, Alcohol, Skin type, Previous sun exposure, Co-morbidities

Radiation will be given through the Film and the Gel as Film has a clinically insignificant bolus effect [4] and the Gel should provide an even thinner layer of silicone on the skin (documents sighted from StrataXRT by the Principle investigator). Both interventions will be applied prophylactically from Day 1 of radiation therapy until all skin reactions have been completely resolved.

## Trial Treatment Regimen (see Figure 1)

Patients will commence RT treatment after having received information about the trial verbally from the radiation oncologist and research radiation therapist (RT)/oncology nurse (ON) and will be given the participant information sheet (**Appendix B).** All participants will give written informed consent **(Appendix C).**

***Randomisation***

At the start of radiation therapy, the chest area to be irradiated will be divided into a medial and lateral half (containing the axilla). The dividing line will be decided by drawing the field border on the skin on Day 1 of treatment and dividing this in half, using permanent markers. Each half will be randomised to either the Film or the Gel. Randomisation will be done by the academic PI, Associate Professor Patries Herst from the University of Otago, Wellington, using computer generated random numbers, provided by the University’s biostatistician, Dr Robin Willink.

Randomisation will be stratified by radiation fractionation regime (26 Gy in 5 fractions, 40Gy in 15 fractions or 50Gy in 25 fractions) and per participating centre to ensure that allocation of Film and Gel over the different regimen and centres is even and to allow for subgroup analysis.

***Application of Mepitel Film***

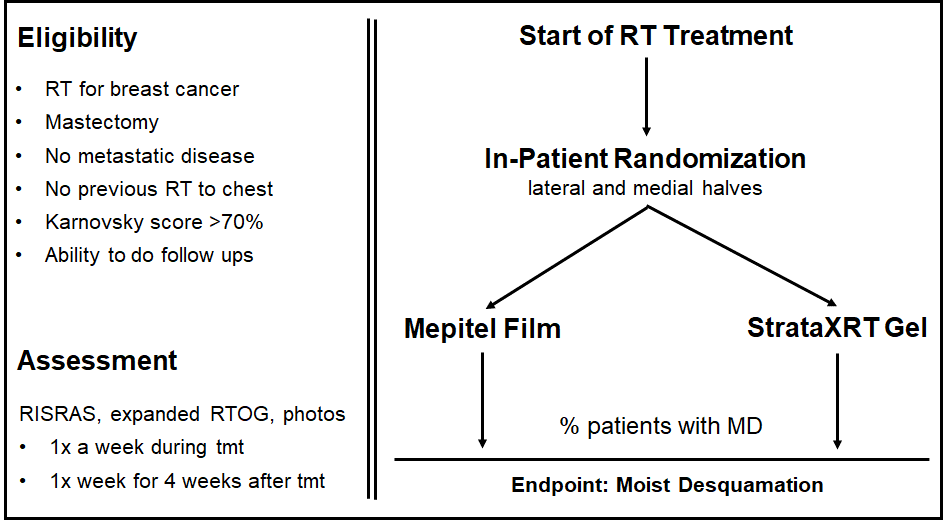
Film will be applied to the trial area as per randomisation by the research radiation therapist/oncology nurse on Day 1 of radiation therapy. Great care must be taken to gently “tap” the film into all the creases of the neck without stretching or overlapping the Film. Film will be replaced by the research radiation therapist/oncology nurse as required, usually once a week but this could be more often.

## *Application of StrataXRT*

## As per company instructions, a small dollop of gel (the size of a finger nail) will be applied twice a day (mornings and evenings) to cover that half of the chest wall randomised to Gel.

***Trial Endpoint:* moist desquamation**

When moist desquamation occurs underneath Film or Gel, the skin will be treated as per department protocol.



**Figure 1. Schematic Diagram of the trial**.

***Measurements***

***Primary outcome measure***

**Incidence of moist desquamation**

This will be scored once a week as measured by 2.5 or greater on RTOG and 1.5 or greater on RISRAS.

The research radiation therapist/oncology nurse is responsible for measuring the incidence of moist desquamation. Moist desquamation is defined as a score of 1.5 or above for moist desquamation on the RISRAS and 2.5 or above for RTOG.

***Secondary outcome measures***

1. **Overall skin reaction severity**

This will be measured as for previous trials using both the Modified RISRAS **(Appendix D)** expanded RTOG **(Appendix D)** to assess the extent of the acute radiation-induced skin reactions in Film and Gel areas. Temporal average and temporal maximum researcher and patient RISRAS scores and temporal maximum RTOG grades will be compared between skin covered by Film and skin covered by Gel.

The research radiation therapist/oncology nurse is responsible for filling out both the researcher component of the RISRAS assessments, which quantify the outward appearance of the skin reaction, and the RTOG evaluations. All scores will be recorded in skin assessment spreadsheets. Patients will be asked to score the patient components of RISRAS for both the Film area and Gel areas on each assessment visit.

**Digital photographs**

Digital photographs of the chest wall will be taken as a visual illustration of the effect of both interventions on skin reactions for further evaluation, in reports, presentations and publications. Photos will be taken in such a way that identification of patients is not possible.

The research radiation therapist/oncology nurse is responsible for taking and storing the digital photographs.

1. **Patient satisfaction**

Patients will be given an exit questionnaire to give them the opportunity to comment on different aspects of participating in the trial (**Appendix E).**

Patients will fill in the exit questionnaires themselves and leave these with the research radiation therapist/oncology nurse at the last assessment visit.

**Withdrawal from the study due to adverse events**

Film and Gel do not contain any components known to have a biological or chemical interaction with skin or with radiation. However, if it is considered necessary to discontinue the use of either Film or Gel because of intolerance, substitution with an alternative treatment will be at the treating clinician’s discretion. In the case of such an event the patient would leave the trial but his/her information would still be part of the analysis up until that point, unless they request that all their information be removed from the database.

1. **Cost analysis**

Direct costs will be determined by the number of Films or tubes of Gel used per patient.

Indirect costs will be determined by the amount of time taken to apply and reapply the Film per patients.

From these, we will determine the total cost per patient for Film and Gel.

**Statistical considerations**

***Participant numbers***

The aim of the trial is to determine if Gel is adequate compared with Film in decreasing the number of women who develop moist desquamation during or immediately after radiation for breast cancer.

If (a) ‘adequate’ means that the probability of developing MD with the Gel is less than **0.075** more than the probability with the film and (b) the probability of declaring it adequate when it is actually inadequate is kept at or below the standard level =**5%** (one-sided) and (c) the probability of developing MD with the Gel is actually **0.03** more than the probability with the film then (d) we need a minimum of **120** women to make the probability of declaring it adequate when it is adequate reach **71%.** So, in this example, we could have **4** more MDs with the Gel than with the Film and the Gel would still be adequate, but with **5** it would be inadequate.

If we factor in a 20% drop-out rate, we would need 145 participants.

***Statistical analysis***

*Baseline Statistics and General Methods*

Baseline characteristics by treatment arm will be summarised in frequency tables and by the use of descriptive statistics for quantitative variables. Summary tables will be prepared giving numbers of patients by treatment arm and by randomisation irregularities, treatment compliance, eligibility infringements, and losses to follow-up (as per CONSORT guidelines).

*Primary outcome: incidence of moist desquamation*

Data are dichotomous: either there is moist desquamation or there is no moist desquamation.We will use standard statistical procedures to obtain confidence intervals for the differences in incidence between Film and Gel. We will use these intervals to conduct the standard hypothesis tests. We will use Fishers exact, Chi-square as appropriate.

*Secondary outcomes*

1. *Overall skin reaction severity*

Data for RISRAS are continuous and the data for the expanded RTOG grading system are categorical with 7 possible categories (0, 1, 1.5, 2, 2.5, 3, 4). We will use the non-parametric Wilcoxon signed ranks test for RISRAS scores and the Chi-squared test for expanded RTOG grades respectively to determine the statistical significance between differences in skin reaction severity in skin areas covered in Film and Gel.

1. *Patient satisfaction: Exit questionnaires*

We will perform a thematic content analysis of answers to the open questions of the exit questionnaires as well as a frequency analysis of Yes/No questions.

***Data Management Plan***

***Identifiable data***

Treatment-related information will be taken from patient hospital notes:

* RT delivery method (3dCRT, IMRT, Intensity Modulated Arc Therapy), RT regime (26Gy in 5 fractions (1 week), 40Gy in 15 fractions (3 weeks) or 50Gy in 25 fractions (5 weeks)), boosts, chemotherapy regime, hormone therapy, surgery.
* Type of cancer, location of primary tumour, TNM Stage
* Patient-related information will be taken from patient hospital notes and from asking the patient at the start of the trial: ethnicity, age, weight, BMI, smoking, alcohol, Fitzgerald skin type, previous sun exposure, co-morbidities (diabetes, heart disease etc).
* Skin reaction information: excel sheets with RISRAS and RTOG scores, digital photographs and exit questionnaires.

All identifiable data will be kept in the patient files as per standard practice in the different Hospitals, with access restricted to the treating doctor and nurses responsible for the patient’s care. No identifiable information will leave the hospital.

***Non-identifiable data***

When the patient enters the trial, she will be given a trial specific number and all other treatment-related, cancer-related and patient-related information will be linked to that number and not to the participant’s name, date of birth etc. This de-identified information will be stored on a password-protected computer in the office of the Principal Investigator at the University of Otago, Wellington for a period of 10 years. Only the research radiation therapists at the hospital will be able to link the de-identified information to you personally. Only the Principal Investigator and the University Biostatistician will have access to your de-identified information.

***References***

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