Pilot Study of KeraStat® Cream for Radiation Dermatitis during Head and Neck Radiotherapy
Wake Forest Baptist Comprehensive Cancer Center
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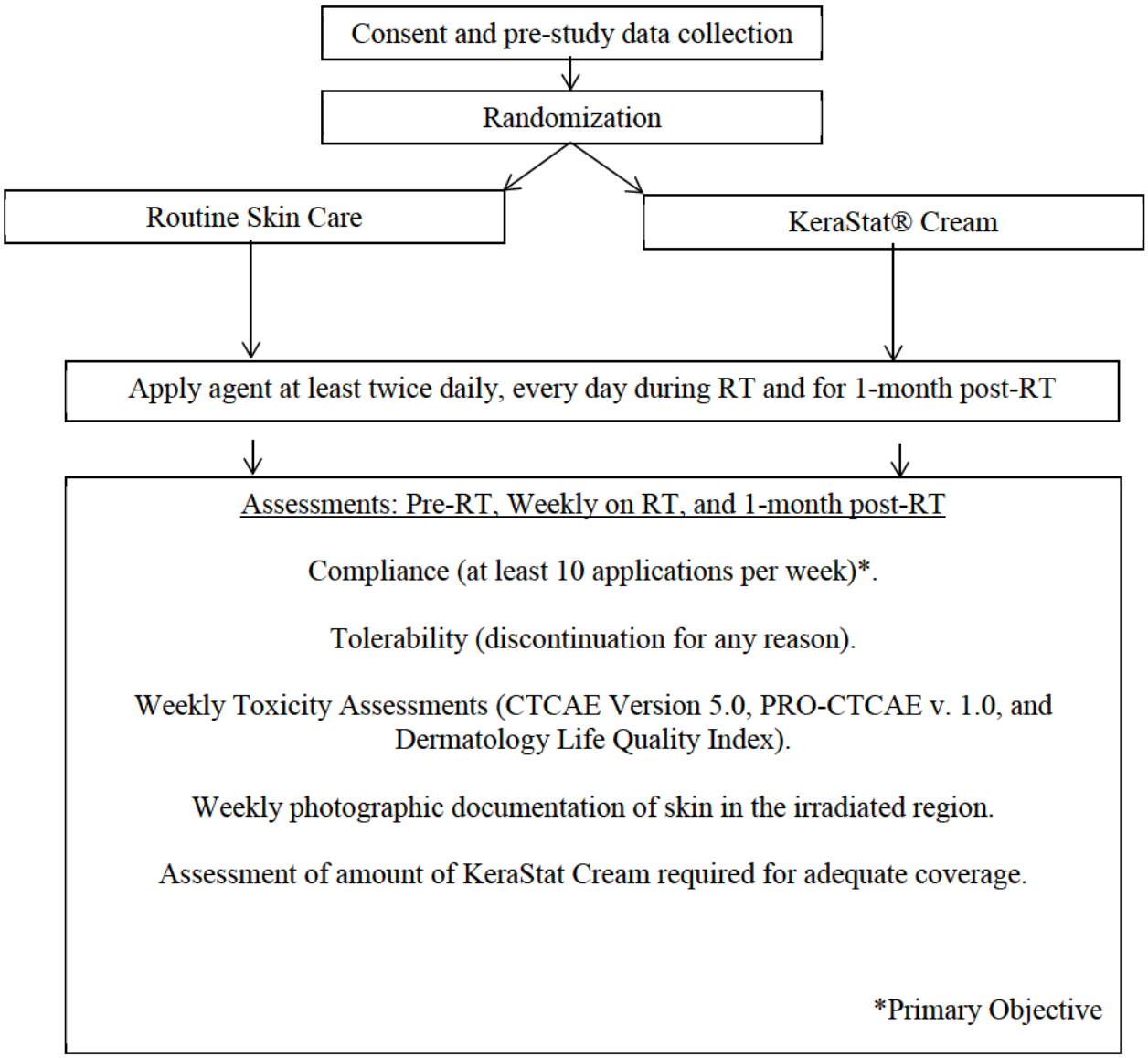
SCHEMA


Consent and pre-study data collection
Randomization
Routine Skin Care
KeraStat® Cream
Apply agent at least twice daily, every day during RT and for 1-month post-RT
Assessments: Pre-RT, Weekly on RT, and 1-month post-RT
Compliance (at least 10 applications per week)*.
Tolerability (discontinuation for any reason).
Weekly Toxicity Assessments (CTCAE Version 5.0, PRO-CTCAE v. 1.0, and Dermatology Life Quality Index).
Weekly photographic documentation of skin in the irradiated region.
Assessment of amount of KeraStat Cream required for adequate coverage.
*Primary Objective

1.0 Introduction and Background

Radiation-induced Skin Reactions in Head and Neck Cancer

Radiotherapy (RT) is an effective intervention for treating head and neck cancer. The primary mechanism of action of RT is to create enough DNA damage within each tumor cell to prevent replication and ultimately induce programmed cell death. This mechanism extends beyond the targeted tumor to normal surrounding tissue. This field effect can be visualized by the effect of RT on the skin within a treatment portal. Approximately 85% of patients undergoing RT experience a moderate-to-severe skin reaction (1), the severity of which can be graded using various scales such as the RTOG toxicity criteria (2) and the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5 (3). The disturbance of the cutaneous barrier function can significantly impact both health-related quality of life and the course of treatment (4). If the skin reaction is severe enough, a treatment break may be recommended (5). Managing the symptoms associated with skin reactions is important for ensuring completion of RT in a timely manner and increasing patient self-esteem (4). Current skin care recommendations typically include the use of non-fragrant, hypo-allergenic moisturizers (4). Further investigations of topical agents to reduce the symptomatic impact of radiation-induced skin reaction are needed.

KeraStat Cream for Radiation-induced Skin Reactions

KeraStat Cream is a non-sterile, non-implantable, emulsion-based wound dressing intended to act as a protective covering in the management of a variety of minor skin wounds and first and second degree (partial thickness) burns as well as skin undergoing radiation treatment. KeraStat Cream uses human hair-derived keratin proteins and is applied topically to the wound surface to absorb exudate, provide a moist environment, and create an environmental barrier supportive of healing. This cream has recently been studied in the breast cancer patient population undergoing radiotherapy to the breast but has not yet been investigated in patients with head and neck cancer being treated with definitive RT.

All ingredients have been used in FDA-approved products. A biological safety profile has been established for the keratin protein ingredient in KeraStat Cream. Biocompatibility studies were chosen and performed in accordance with ISO 10993-1:2007, “Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.” This testing included a full toxicological risk assessment per ISO 10993-17 and 10993-18. KeraStat® Cream has been subjected to a human subject Repeat Insult Patch Test (RIPT) to evaluate the irritation/sensitization potential of the product when applied to uncompromised skin. No adverse skin reactions were observed in 50 subjects evaluated in the RIPT study, and KeraStat Cream was considered a non-primary irritant and non-primary sensitizer to the skin. Additionally, KeraStat® Gel, an FDA-approved hydrogel wound dressing containing the keratin proteins, water, and a preservative, was tested in compromised skin to assess human sensitization study, the Skin Prick Test (SPT). The results of the SPT demonstrated that there was no humoral immune response to keratin and supported pre-clinical testing, which determined that the product would not elicit an immune response.

The current study is considered a nonsignificant risk (NSR) device study according to Food and Drug Administration (FDA) guidance and does not require an Investigational Device Exemption (IDE) in advance of study conduct. NSR device studies must follow the abbreviated requirements presented in 21 CFR 812.2(b) related to labeling, Institutional Review Board (IRB) approval, informed consent, monitoring, records, reports, and prohibition against promotion.

Study Rationale

Although well tolerated by most patients, about 30% of patients undergoing RT develop a Grade 2 or worse early adverse skin reaction (EASR). One study in Taiwan showed 23% of patients undergoing chest wall or whole breast irradiation developed moist desquamation based on the RTOG scale (6). This scale described grade 2 skin toxicity as tender or bright erythema, patchy moist desquamation / moderate erythema; Grade 3 skin toxicity was described as confluent moist desquamation other than skin fold, pitting edema. Both grade 2 and 3 skin toxicities were recorded in the assessment of patients in the Taiwanese study. Another study comparing breast intensity-modulated radiotherapy (IMRT) to conventional tangent fields showed a decrease in moist desquamation, as defined by the NCI CTCAE version 2, from 48% to 31% of patients, suggesting that even with advanced treatment techniques, a significant number of patients experience skin toxicity (7).

Beyond the discomfort patients may experience, EASRs may result in poor patient outcomes. Severe EASRs can require a "treatment break" which, in some cancers, may result in incomplete tumor control and greater chance of local recurrence and lower survival rates. In addition to the potential impact on cancer outcomes, EASRs may affect patients' self-esteem due to the appearance of their skin and recovery time after treatment. Standard skin regimens often include routine application of creams or lotions in an effort to combat the dryness, prevent interruption of the skin's natural barrier (e.g., cracking or flaking), and reduce the appearance of inflammation. Patients often begin using these creams/lotions at the start of RT. Providing patients with a product that moisturizes and reduces the appearance of inflammation may improve patients' satisfaction with their appearance as they progress through RT treatment.

The investigators have demonstrated the feasibility of KeraStat cream during breast RT for patients with breast cancer [data not published]. This study represents a subsequent step to confirm the feasibility of extending comparative studies of KeraStat cream versus routine skin care to patients with a different primary cancer site (head and neck cancer). Due to significant differences in the nature of the head and neck cancer treatment, including the higher risk of high-grade radiation dermatitis experienced by head and neck cancer patients, it is first necessary to confirm the feasibility and tolerability of KeraStat cream in these patients. These data would then directly inform randomized, comparative studies to evaluate the efficacy of KeraStat cream to reduce radiation dermatitis for patients receiving head and neck RT.

KeraNetics has determined that this study is a non-significant risk study under 21 CFR 812.3(m). This device is not intended as an implant. It is not for use supporting or sustaining human life. It is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health, and it does not

otherwise present a serious risk to health, safety, or welfare of a subject. Furthermore, KeraStat® Cream is classified as a wound dressing; wound dressings are classified as nonsignificant risk devices in FDA's "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies" published January 2006.

2.0 Objectives

This is a single site, randomized, open-label comparison pilot study to assess the feasibility and effectiveness of KeraStat Cream compared with routine skin care (RSC) in managing RT-induced early adverse skin reaction (EASR) in patients undergoing RT to the head and/or neck.

Hypothesis: The use of KeraStat Cream in patients receiving radiotherapy for head and neck is feasible, tolerable, and reduces the severity of EASR in the treated region of interest.

2.1 Primary Objective(s)

To determine the feasibility of the use of KeraStat Cream in patients receiving radiotherapy for head and neck cancer.

2.2 Secondary Objective(s)

2.2.1 To determine the tolerability of KeraStat Cream in patients receiving radiotherapy for head and neck cancer compared to routine skin care.

2.2.2 To assess the effectiveness of KeraStat Cream in reducing the severity of EASR in patients receiving radiotherapy for head and neck cancer, compared to routine skin care. This will be performed by evaluating:

2.2.2.1 Objective evaluation of EASR using the CTCAE Version 5.0 scale of radiation dermatitis,

2.2.2.2 Patient-reported outcomes of radiation dermatitis using the PRO-CTCAE version 1.0, and

2.2.2.3 Dermatologic-specific quality of life assessment

2.2.3 To estimate the amount of KeraStat Cream used per patient and coverage on the skin.

3.0 Patient Selection

3.1 Inclusion Criteria

3.1.1 Diagnosis of head and neck cancer planned to receive conventionally-fractionated definitive radiotherapy to the head and neck to a total prescribed dose of at least 60 Gy

3.1.2 Able and willing to sign protocol consent form

3.1.3 Able and willing to complete tolerability and quality of life assessments

3.1.4 Able and willing to have photographs of the affected area taken regularly

3.2 Exclusion Criteria

3.2.1 Women who are pregnant, lactating/nursing or plan to become pregnant

3.2.2 Previous radiation therapy to the area to be treated with radiation therapy

3.2.3 Active, medically necessary use of topical corticosteroids in the irradiation area

3.2.4 Active scleroderma or lupus requiring systemic medication

3.2.5 Treatment with anti-EGFR antibodies for head and neck cancer (previously or planned)

3.3 Inclusion of Women and Minorities

Men and women of all races and ethnicities who meet the above-described eligibility criteria are eligible to participate in this study. The study consent form will also be provided in Spanish for Spanish-speaking participants.

Based on WFBCCC population estimates, we may expect approximately 20% of participants to be women. Translating this to our sample size estimate of 22 patients, we may enroll approximately 4-5 women. We may enroll approximately 10-13% Black or African American patients. Based on our catchment area and hospital demographics we do not expect high accruals of individuals of Hispanic/Latino, American Indian/Alaska Native or Asian ancestry; however, no individual will be excluded from the study if they satisfy the above inclusion/exclusion criteria. Should we not meet or exceed these estimates, the PI will engage the Office of Cancer Health Equity to discuss strategies to enhance recruitment in these target populations.

4.0 Registration Procedures

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be linked to the study in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix A)
2. Complete the Protocol Registration Form (Appendix B)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

   Contact Information:
   Protocol Registrar PHONE (336) 713-6767
   Protocol Registrar FAX (336) 713-6772
   Protocol Registrar E-MAIL (registra@wakehealth.edu)

   *Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

   Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- randomize the patient
- register the patient on the study

5.0 Study Outcomes and Study Measures

5.1 Primary Outcome

Feasibility of use of KeraStat Cream is measured by patience compliance with directions for use.

5.2 Secondary Outcomes

5.2.1 Tolerability is measured by the number of patients who discontinue skin care regimen due to intolerance for any reason.

5.2.2 The effectiveness of KeraStat Cream in reducing EASR will be assessed as follows:

5.2.2.1 Objective assessment of EASR, defined as Grade 2+ using the CTCAE version 5.0 scale of radiation dermatitis (Appendix H)

5.2.2.2 Patient-reported assessment of skin toxicity using the PRO-CTCAE version 1.0 scale of radiation skin reaction (Appendix H)

5.2.2.3 Dermatologic-specific quality of life will be measured using the Dermatology Life Quality Index (Appendix I)

5.2.3 Skin coverage by the will be calculated the number of tubes of KeraStat Cream used.

6.0 Treatment Plan

6.1 Study Design

This is a single site, randomized, open-label comparison pilot study to assess the feasibility and effectiveness of KeraStat Cream in managing RT EASR in patients undergoing RT to the head and neck. Sufficient subjects will be screened such that 24 total subjects will complete the study. Patient compliance is expected to be good, so a target recruitment of 28 subjects is anticipated. Patients will be screened for inclusion at their consultation visit in the WFBCCC Department of Radiation Oncology. A total of 28 head and neck cancer patients to receive definitive RT will be recruited and consented.

After informed consent, the patient will be registered to the study and randomized to either routine skin care (RSC) or KeraStat study arms. Patients randomized to the KeraStat arm will be provided with KeraStat Skin Cream for application as often as needed but at least twice daily, morning and evening. Baseline pre-RT assessments will be completed prior to the initiation of RT. These can be completed on the date of RT treatment planning CT simulation scan or later during the radiation treatment-planning process (generally 1.5-2 weeks).

Patients are generally treated with RT using daily fractions delivered Monday through Friday, with weekends and holidays off, for approximately 6-7 weeks. Generally, radiation treatment breaks should be avoided whenever possible, but treatment breaks deemed necessary by the treating radiation oncologist are acceptable and will be recorded, as will the indication for the treatment break. While on treatment, patients are seen by the radiation oncologist (and possibly other support staff including but not limited to nurses, speech language pathologists, dieticians, navigators and case workers) once weekly as part of a routine on-treatment visit. The purpose of this visit is to review the patient's treatment course, monitor for expected and unexpected toxicity, and manage the patient appropriately.

Patients who receive definitive RT receive chemotherapy. Cisplatin is preferred if medically possible, with other cytotoxic regimens acceptable at the discretion of the medical oncologist. Anti-EGFR antibody therapy (i.e. cetuximab) is not permitted.

At weekly on-treatment visits, study evaluations of the skin in the region of interest will occur. These will include objective assessments by study staff, photographs, patient-reported assessments of the skin and a dermatologic-specific quality of life questionnaire. The radiation oncologist will see each patient along with study staff in follow-up 4 weeks after completing RT to assess the patient for RT-induced skin and other toxicities that may have occurred.

6.2 Treatment Administration

Beginning on the first day of RT, patients will be instructed to apply skin care according to their randomization arm (Section 6.2.1). The patient will be instructed to apply the assigned agent every day as needed, but at least twice daily, to the skin of the head and neck within the region of interest.

6.2.1 Randomization

All subjects will be randomized to receive one of two test agents: KeraStat Cream or routine skin care (RSC).

6.2.2 Investigational Agent

KeraStat Cream is a non-sterile, non-implantable, emollient-based wound dressing intended to act as a protective covering in the management of a variety of skin conditions.

6.2.3 Routine Skin Care

Routine skin care will include various standard-of-care, commercially available agents. A list of example agents will be provided to patients in this arm (Appendix J).

6.3 General Concomitant Medication and Supportive Care Guidelines

Concomitant medications are permitted during this study unless otherwise specified in the Exclusion Criteria.

Patients should receive *full supportive care*, including transfusions of blood and blood products, erythropoietin, antibiotics, antiemetics, etc., as clinically indicated. Anti-inflammatory or narcotic analgesics may be offered as needed. Medications considered necessary for the patient's well-being may be given at the discretion of the investigator, i.e., chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems, etc. The reason(s) for treatment, dosage, and dates of treatment should be recorded on the flow sheets.

6.4 Duration of Therapy

Skin care with the assigned agent will be continued until the end of the study period (1 month after end of RT). Study cream will be discontinued if the patient cannot tolerate the agent or if adverse events related to the study agent occur.

6.5 Duration of Follow Up

Patients will be followed for a minimum of 1-month after the completion fo radiotherapy for adverse events monitoring.

6.6 Criteria for Removal from Study

A documented effort must be made to determine why a subject fails to return for the necessary visit or is dropped from the study, and the reason for withdrawal must be recorded in the source documents and case report form (CRF). A subject may withdraw or be removed from the study for any of the following reasons and will be treated as considered appropriate by the Investigator:

- Subject request (for any reason)
- In the opinion of the Investigator, continuation is not in the best interest of the subject
- A serious or unexpected AE occurs such that continuation in the study is inappropriate
- Pregnancy
- RT is stopped

If a subject is prematurely discontinued from participation in the study for any reason, the Investigator must follow up on all ongoing adverse events (if any).

In the event a subject is prematurely discontinued from the study due to an AE, or unexpected AE or serious adverse event (SAE) (as defined in Section 11.5.1), the procedures stated in Sections 11.3-11.9 must be followed.

7.0 Study Assessments

7.1 Study Assessment Visits

7.1.1 Baseline Visit

After informed consent, registration and randomization, study staff will collect baseline demographic information. This includes information such as age, gender, race/ethnicity, medical history, current medications, allergy history. The skin within the region of

interest will be photographed. Study personnel will collect a baseline skin toxicity assessment (Appendix H). Subjects will complete the Dermatology Life Quality Index (Appendix I).

The baseline assessment may occur at any time between registration and the first radiation treatment. A convenient visit may include the radiation treatment planning CT simulation, which occurs in the Department of Radiation Oncology approximately 1.5-2 weeks prior to the start of RT. At this visit, patients may be approached for the baseline assessment. This will be coordinated by study staff.

7.1.2 Weekly Visits During RT

During regular visits with medical staff, study subjects will also meet with study staff. Study staff will obtain photographs of the area of irradiation. Study staff will obtain photographs of the area of irradiation. Study personnel will collect the skin toxicity assessment (Appendix H). Any adverse events will be noted and addressed. Subjects will complete the Dermatology Life Quality Index (Appendix I). Study personnel will provide KeraStat Cream, as needed, to subjects randomized to receive KeraStat Cream. Subjects randomized to standard of care will follow the instructions of their radiation oncologist.

7.1.3 Post-Radiation Therapy Visit

During a final follow up visit with medical staff (estimated at 4 to 6 weeks post radiation therapy termination), or if the subject terminates the study, the study subject will meet with study staff. Study staff will obtain photographs of the area of irradiation. Study personnel will collect the skin toxicity assessment (Appendix H). Any adverse events will be noted and addressed. Subjects will complete the Dermatology Life Quality Index (Appendix I).

7.2 Study Calendar

	Prior to RT Start	Weekly During RT[a]	1-month Follow-up Visit
Informed consent	X		
Demographics (Appendix B, C, D)	X		
Medical history (Appendix E)	X		
Medications (Appendix F)	X		
Compliance & Tolerability Assessment (Appendix G)	X	X	X
Toxicity Assessment Form (Appendix H)	X	X	X
Dermatology Life Quality Index (Appendix I)	X	X	X
Photographic Documentation of the Skin in the Region of Interest	X	X	X

[a] Assessments may occur within +/- 5 days of weekly on-treatment visit. On-treatment visits occur weekly until patient has completed (or stopped) treatment. If treatment breaks are necessary, patient may be seen on weeks 8 or 9 if needed.
[b] Post-treatment assessments may occur within +/- 2 weeks of scheduled time point

8.0 Adverse Events List and Reporting Requirements

8.1 Adverse Event Definitions

8.1.1 Adverse Event (AE)

An adverse event (AE) is defined as any unfavorable or unintended dermatological condition.

8.1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is any untoward medical occurrence that occurs irrespective of study treatment assignment, if it satisfies any of these criteria: results in death; is life-threatening; requires inpatient hospitalization or prolongs existing hospitalization; results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions; or if the event results in a congenital anomaly or birth defect.

8.1.3 Adverse Event Reporting

Subjects will be encouraged to spontaneously report any changes in baseline health from the time the subject enters the study through study completion.

Study staff also will inquire about AEs on each visit while the subject is in the research center.

8.1.4 Assessment of Causality

The Investigator is obligated to assess the relationship between study device and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study device will be considered and investigated.

The Investigator will assess causality based on the following definitions:

- Not Related (the AE was more likely explained by causes other than the study treatment).
- Related (the study treatment and AE were closely related in time and the AE may be explained by exposure to study product: e.g., known adverse effect or recurrence on re-challenge).

8.2 Recording Adverse Events

When an AE occurs, it is the responsibility of the Investigator to review all documentation (e.g., medical progress notes, laboratory, and diagnostics reports) relative to the event. The Investigator will then record all relevant information regarding an AE in the CRF.

The Investigator will attempt to establish a diagnosis of the AE based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

8.2.1 Eliciting Adverse Event Reports

At each visit, subjects will be asked about AEs by means of a non-leading question, such as “how have you been since your last visit?” or “how has the treatment been?” In this way, possibly milder, but clinically important, side effects of the study device can be detected. SAEs will be reported promptly to KeraNetics as described in the following table once the Investigator determines that the event meets the protocol definition of a SAE.

8.3 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only.

- **Attribution** of the AE:

- Definite – The AE **is clearly related** to the study treatment.
- Probable – The AE **is likely related** to the study treatment.
- Possible – The AE **may be related** to the study treatment.
- Unlikely – The AE **is doubtfully related** to the study treatment.
- Unrelated – The AE **is clearly NOT related** to the study treatment.

8.4 STRC SAE Reporting Requirements

The Data Safety Monitoring Committee (DSMC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix K. All Adverse Events that occur during protocol intervention and are coded as either 1) unexpected grade 4, 2) unplanned inpatient hospitalization ≥ 24 hours (regardless of grade), or grade 5 (death) must be reported to the DSMC using the using the SAE console in WISER.

All WFBCCC Clinical Protocol and Data Management (CPDM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for DSMC reporting are responsible for informing a clinical member of the DSMC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

8.5 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

9. STUDY DEVICE MATERIALS AND MANAGEMENT

9.1 Study Device

KeraStat Cream is a non-sterile, non-implantable, emollient-based wound dressing intended to act as a protective covering in the management of a variety of skin conditions. KeraStat Cream is designed to be topically applied to the skin surface. When applied, KeraStat Cream covers the skin or wound, isolating it from the external environment, absorbing excess exudate and facilitating a moist wound environment.

9.2 Study Device Packaging and Labeling

KeraStat Cream will be provided in multiuse tubes. The study device supplies will be maintained at the site under controlled conditions and dispensed by qualified personnel at the study site. The study device labels will contain information to meet the applicable regulatory requirements.

9.3 Study Device Storage

The study device must be stored at room temperature (15 to 30°C [59-86°F]). The study device must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive the study device, in accordance with all applicable regulatory requirements. Only authorized site staff may supply the study device.

9.4 Study Device Preparation

KeraStat Cream final product will be manufactured within applicable current Good Manufacturing Practice (cGMP) regulations in accordance with KeraNetics quality system. The product will be supplied in the form of a cream and packaged in a multi-use tube as detailed in Section 9.2.

9.5 Administration

KeraStat Skin Cream has been shown to moisturize the skin and reduce dryness, redness, and the appearance of inflammation. It should be applied **as needed** but **at least twice daily**.

In this study, patients will apply the cream at least twice-daily during the radiation treatments, 7 days per week.

9.6 Study Device Accountability

The Investigator is responsible for the study device accountability and record maintenance.

9.7 Study Device Handling and Disposal

Unused supplies, including the study device, will be disposed of using appropriate documentation according to International Conference on Harmonization-Good Clinical Practice (ICH-GCP), local requirements, applicable Occupational Safety and Health Administration (OSHA) and Environmental Protection Agency (EPA) regulations, and applicable study-specific procedures.

10.0 Data Management

Informed consent document	WISER
Protocol registration form	WISER
Appendix C	REDCap
Appendix D	REDCap
Appendix E	REDCap
Appendix F	REDCap
Appendix G	REDCap
Appendix H	REDCap
Appendix I	REDCap
Photographic Documentation of Skin in the Region of Interest	REDCap

11.0 Statistical Considerations

11.1 Analysis of Primary Objective

The completion rate will be used as a measure of feasibility, with participants with an average of 10 or more applications per week being classified as compliant. In each arm, a 95% confidence interval will be calculated around the estimate of compliance.

11.2 Analysis of Secondary Objective

11.2.1 The rate of discontinuation for any reason will be used as a measure of tolerability, with patients who do not discontinue the skin care regimen being classified as tolerant. In each arm, a 95% confidence interval will be calculated around the estimate of tolerability.

11.2.2 Proportion of EASR (CTCAE v5.0 Grade 2+ radiation dermatitis) will be compared between the KeraStat group and the RSC group at the end of treatment, using a Fisher's exact test.

11.2.3 Mean scores of the modified PRO-CTCAE patient-reported outcome scales collected each week over the 6-7 weeks of radiation therapy and at the one-month post treatment follow-up visit will be compared between the KeraStat and RSC groups using a simple repeated measures analysis of variance model with treatment group as the independent variable of interest.

11.2.4 Mean DLQI score at each time point will be compared between the KeraStat and RSC groups, again using a simple repeated measures analysis of variance model with treatment group as the key independent variable. Additionally, the mean of the highest DLQI score across all time points will be compared between the KeraStat and RSC groups using a t-test.

11.2.5 Skin coverage (calculated as number of tubes of KeraStat Cream used per week) will be summarized with a frequency distribution and computation of central tendency and variability (mean, median, and standard deviation).

11.3 Power and Sample Size

Up to 28 subjects will be enrolled on this pilot study to assure retention of at least 24 complete, evaluable subjects for the primary endpoint. The expected accrual rate is four per month with accrual lasting approximately six months. Participants will be randomized equally (n=12 per group) to standard of care or KeraStat Cream. With 12 participants in each treatment group expected to complete the study, we will be able to calculate a 95% confidence interval around the compliance rate in each group with a

maximum total confidence interval width of 0.578 (this maximum occurs if the compliance proportion is 0.5).

11.4 Estimated Accrual Rate

At the Wake Forest Baptist Comprehensive Cancer Center, we see approximately 320 new cases of pharyngeal, oral cavity and laryngeal cancers per year. Internal metrics within the Radiation Oncology Department have identified an average rate of 6.4 new patients starts over the last 3 years. This has increased to 8.3 new patient starts per month over the last 9 months (January-August 2019). As such, we expect a patient accrual rate of approximately 4 patients per month.

11.5 Estimated Study Length

The study period includes the duration of radiation therapy (6-7 weeks) plus an additional 4-weeks of follow-up. We anticipate to accrue approximately 2-4 patients per month and to complete all study follow-up in approximately 6-13 months.

References

1. Salvo N, Barnes E, van Draanen J, Stacey E, Mitera G, Breen D, et al. Prophylaxis and management of acute radiation-induced skin reactions: a systematic review of the literature. Curr Oncol. 2010;17(4):94-112.
2. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31(5):1341-6.
3. National Cancer Institute DoCTDNIoH, U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.02009.
4. Bensadoun RJ, Humbert P, Krutman J, Luger T, Triller R, Rougier A, et al. Daily baseline skin care in the prevention, treatment, and supportive care of skin toxicity in oncology patients: recommendations from a multinational expert panel. Cancer Manag Res. 2013;5:401-8.
5. Glover D, Harmer V. Radiotherapy-induced skin reactions: assessment and management. Br J Nurs. 2014;23(4):S28, S30-5.
6. Chen MF, Chen WC, Lai CH, Hung CH, Liu KC, Cheng YH. Predictive factors of radiation-induced skin toxicity in breast cancer patients. BMC Cancer. 2010;10:508.
7. Pignol J-P, Olivotto I, Rakovitch E, Gardner S, Sixel K, Beckham W, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. J Clin Oncol. 2008;26(13):2085-92.

Appendix A – Eligibility Checklist

IRB Protocol No. IRB00062012	WFBCCC Protocol No. 97319
Study Title: Pilot Study of KeraStat Cream for Radiation Dermatitis during Head and Neck Radiotherapy	
Principal Investigator: Ryan Hughes, MD	

Inclusion Criteria (as outlined in study protocol)	Criteria is met	Criteria is NOT met	Source Used to Confirm * (Please document dates and lab results)
Diagnosis of head and neck cancer planned to receive conventionally-fractionated definitive radiotherapy to the head and neck to a total prescribed dose of at least 60 Gy	☐	☐	
Able and willing to sign protocol consent form	☐	☐	
Able and willing to complete tolerability and quality of life assessments	☐	☐	
Able and willing to have photographs of the affected area taken regularly	☐	☐	
Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm * (Please document dates and lab results)**
Women who are pregnant, lactating/nursing or plan to become pregnant	☐	☐	
Previous radiation therapy to the area to be treated with radiation therapy	☐	☐	
Active, medically necessary use of topical corticosteroids in the irradiation area	☐	☐	
Active scleroderma or lupus requiring systemic medication	☐	☐	
Treatment with anti-EGFR antibodies for head and neck cancer (previously or planned)	☐	☐	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

OnCore Assigned PID: ___ ___ ___ ___ ___ ___ ___ ___

Signature of research professional confirming eligibility: _____

Date: ___ ___ / ___ ___ / ___ ___

Signature of Treating Physician: _____

Date: ___ ___ / ___ ___ / ___ ___

Signature of Principal Investigator**: _____

Date: ___ ___ / ___ ___ / ___ ___

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: “Pathology report, 01/01/14” or “Clinic note, 01/01/14”

**Principal Investigator signature can be obtained following registration if needed

Appendix B – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___

ZIPCODE: ___ ___ ___ ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic ☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2

Primary Diagnosis:

_____

Date of Diagnosis: ___ ___ /___ ___/___

Performance Status: ___ ECOG

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by OnCore): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.

Compete the eligibility checklist in WISER and then give the completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-713-6772 or registra@wakehealth.edu, respectively.

Appendix C - Race & Ethnicity Verification Form

Thank you so much for helping us to verify your race and ethnicity to ensure the quality of our information. As a brief reminder, the information you provide today will be kept confidential.

1. Are you:
   - ☐ Hispanic or Latino/a
   - ☐ Not Hispanic or Latino/a

2. What is your race? One or more categories may be selected.
   - ☐ White or Caucasian
   - ☐ Black or African American
   - ☐ American Indian or Alaskan Native
   - ☐ Asian
   - ☐ Native Hawaiian or Other Pacific Islander
   - ☐ Other, Please Specify: _____

Internal use only:

Name: _____ MRN#: _____

Was the self-reported race and ethnicity of the participant verified at the time of consent?
☐ **Yes** ☐ **No**

Was a discrepancy found? **Yes** ☐ **No** ☐
If yes, please provide what is currently indicated in the EMR:
Ethnicity: _____ Race: _____

Additional comments:
_____

_____

_____

Appendix D – Demographic and Health Behaviors

Form should be given to the participant to complete.
The following questions will ask about your demographic background and your health behaviors. There are no "right" or "wrong "answers to these questions. The information you provide will remain strictly confidential.

1. How confident are you filling out medical forms by yourself?
   - □ Extremely
   - □ Quite a bit
   - □ Somewhat
   - □ A little bit
   - □ Not at all

2. What is your ethnicity?
   - □ Hispanic or Latino
   - □ Not Hispanic or Latino

3. What is your race? One or more categories may be selected. Mark all that apply.
   - □ White
   - □ Black or African American
   - □ American Indian or Alaskan Native
   - □ Asian
   - □ Native Hawaiian or other Pacific Islander
   - □ Other → Please specify: _____
   - □ Prefer not to answer

4. What is your current marital status?
   - □ Married
   - □ Living as married
   - □ Divorced
   - □ Widowed
   - □ Separated
   - □ Single, never been married
   - □ Prefer not to answer

5. What is the highest grade or level of schooling you completed?
   - □ Less than 8 years
   - □ 8 through 11 years
   - □ 12 years or completed high school
   - □ Post high school training other than college (vocational or technical)
   - □ Some college
   - □ College graduate
   - □ Postgraduate
   - □ Prefer not to answer

6. During the past 4 weeks, did you have enough money to meet the daily needs of your family?
   - □ Yes
   - □ No

<u>Section 2</u>: The next section will ask you some questions about your physical activity.

Physical activities are activities where you move and increase your heart rate above its resting rate, whether you do it for pleasure, work or transportation. The following questions ask about the amount and intensity of physical activity you usually do. The intensity of an activity is related to the amount of energy you use to do these activities.

Examples of physical activity intensity levels:

Light activities • your heart beats slightly faster than normal • you can talk and sing	 Walking Leisurely  Stretching  Vacuuming or Light Yard Work
Moderate activities • your heart beats faster than normal • you can talk but not sing	 Fast Walking  Aerobics Class  Strength Training  Swimming Gently
Vigorous activities • your heart rate increases a lot • you can't talk or your talking is broken up by large breaths	 Stair Machine  Jogging or Running  Tennis, Racquetball, Pickleball or Badminton

7. How physically active are you? (check one answer on each line)

	Does this accurately describe you?	
a) I rarely or never do any physical activities.	Yes □	No □
b) I do some **light** or **moderate** physical activities, but not every week.	Yes □	No □
c) I do some **light** physical activity every week.	Yes □	No □
d) I do **moderate** physical activities every week, but less than 30 minutes a day or 5 days a week.	Yes □	No □
e) I do **vigorous** physical activities every week, but less than 20 minutes a day or 3 days a week.	Yes □	No □
f) I do 30 minutes or more a day of **moderate** physical activities, 5 or more days a week.	Yes □	No □
g) I do 20 minutes or more a day of **vigorous** physical activities, 3 or more days a week.	Yes □	No □

<u>Section 3</u>: This section will ask you some questions about smoking. For the questions below, please try to select a single number.

8. Have you smoked at least 100 cigarettes (5 packs=100 cigarettes) in your entire life?
   - □ Yes
   - □ No ➡ Go to Question 12.
   - □ Don't know / Not sure ➡ Go to Question 12

9. How many total years have you smoked (or did you smoke) cigarettes? Do not count any time you may have stayed off cigarettes.
   _____ Years *If you smoked less than one year, write "1."*

10. On average when you have smoked, about how many cigarettes do you (or did you) smoke a day?
    A pack usually has 20 cigarettes in it.
    _____ Number of cigarettes per day

11. How long has it been since you last smoked a cigarette (even one or two puffs)? *First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.*

- □ I smoked a cigarette today (at least one puff).
- □ 1-7 days ➡ Number of days since last cigarette: _____
- □ Less than 1 month ➡ Number of weeks since last cigarette: _____
- □ Less than 1 year ➡ Number of months since last cigarette: _____
- □ More than 1 year ➡ Number of years since last cigarette: _____
- □ Don't know / Don't remember.

12. Which of the following phrases best characterizes you at this time? *(Please mark only one response.)*

- □ Normal, no complaints, no symptoms of disease
- □ Able to carry on normal activity, minor symptoms of disease
- □ Normal activity with effort, some symptoms of disease
- □ Care for self, unable to carry on normal activity or to do active work
- □ Require occasional assistance but able to care for most of personal needs
- □ Require considerable assistance for personal care
- □ Disabled, require special care and assistance
- □ Severely disabled, require continuous nursing care

How many times have you fallen in the last 6 months? ____ times

Appendix E – Medical History

Study Number: ___ ___ ___ ___ ___ **PID:** ___ ___ ___ ___ ___ ___ ___ ___ ___

PI: _____ **Date (mm/dd/yy):** ___ ___/___ ___/ ___ ___

To be completed by research nurse.

Patient Age: _____

Primary Cancer Site: _____
Ex: oropharynx, larynx, hypopharynx, nasopharynx, oral cavity, sinus,

Primary Cancer Laterality (circle):

LEFT RIGHT BILATERAL Not Applicable/Unknown

Clinical Stage: _____ T Stage: _____

N Stage: _____ M Stage: _____

Surgery for this cancer prior to radiotherapy: ☐ YES ☐ NO

Medical history

Weight (kg): _____ Body mass index (kg/m2): _____

- ☐ Diabetes If yes: ☐ insulin-dependent or ☐ non-insulin dependent
- ☐ Coronary artery disease
- ☐ Heart attack / myocardial infarction (MI)
- ☐ Peripheral Vascular Disease
- ☐ Cerebrovascular Disease / History of stroke / cerebrovascular accident (CVA)
- ☐ Chronic Obstructive Pulmonary Disease (COPD)
- ☐ Immunosuppression

Allergies (list): _____

_____

_____

_____

Appendix F – Current Medications Form

Study Number: ___ ___ ___ ___ ___ **PID:** ___ ___ ___ ___ ___ ___ ___ ___ ___

PI: _____ **Date (mm/dd/yy):** ___ ___/___ ___/___ ___ ___ ___

Instructions: Fill this form out at the baseline/pre-study visit. To be completed by research nurse.

Medications List

Prescription Medications:

Name of Medication	Dose	Units	Frequency	Condition Medication Taken For	Start date (mm/dd/yy)	Stop date (mm/dd/yy)	Formulation	Route	Notes

Appendix G – Compliance and Tolerability Assessment Form

Study Number: ___ ___ ___ ___ ___ **PID:** ___ ___ ___ ___ ___ ___ ___ ___ ___

PI: _____ **Date (mm/dd/yy):** ___ ___/___ ___/ ___ ___

To be completed by research nurse.

Name of Person Completing Form: _____

Time Point (select one where applicable):

☐ Baseline (Pre-RT)

☐ Week 1 ☐ Week 2 ☐ Week 3 ☐ Week 4

☐ Week 5 ☐ Week 6 ☐ Week 7 ☐ Week 8 ☐ Week 9

☐ 1-month Post-RT Follow-up

Number of Applications in the Last Week: _____
- May be calculated by multiplying the average number of applications per day in the prior week by 7
- (Not applicable or N/A for baseline visit)

Number of Tubes Used in the Last Week: _____

Did the patient discontinue application of study-assigned cream in the preceding week? (select one)

YES NO

If yes, what was the reason for discontinuation of the study-assigned cream?

_____

_____

_____

Appendix H – Toxicity Assessment Form

Study Number: ___ ___ ___ ___ ___ **PID:** ___ ___ ___ ___ ___ ___ ___ ___ ___

PI: _____ **Date (mm/dd/yy):** ___ ___/___ ___/ ___ ___

To be completed by research nurse:

Name of Person Completing Form: _____

Time Point (select one where applicable):

☐ Baseline (Pre-RT)

☐ Week 1 ☐ Week 2 ☐ Week 3 ☐ Week 4

☐ Week 5 ☐ Week 6 ☐ Week 7 ☐ Week 8 ☐ Week 9

☐ 1-month Post-RT Follow-up

To be completed by research nurse and confirmed by treating radiation oncologist:

Radiation Dermatitis Scale

CTCAE Version 5.0 Grade	Definition	Present (Check one that best applies)
0	None	
1	Faint erythema or dry desquamation	
2	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	
3	Moist Desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	
4	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	
5	Death	

Oral Mucositis Scale

CTCAE Version	Definition	Present (Check one

5.0 Grade		that best applies)
0	None	
1	Asymptomatic or mild symptoms; intervention not indicated	
2	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	
3	Severe pain; interfering with oral intake	
4	Life-threatening consequences; urgent intervention indicated	
5	Death	

PRO-CTCAE Symptom Assessment

To be completed by the patient.

25. PRO-CTCAE™ Symptom Term: Skin dryness				
a. In the last 7 days, what was the SEVERITY of your DRY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

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

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

37. PRO-CTCAE™ Symptom Term: Skin darkening	
a. In the last 7 days, did you have any UNUSUAL DARKENING OF THE SKIN?	
O Yes	O No

3. PRO-CTCAE™ Symptom Term: Mouth/throat sores				
a. In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
b. In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

Appendix I – Dermatology Life Quality Index

Study Number: ___ ___ ___ ___ ___ **PID:** ___ ___ ___ ___ ___ ___ ___ ___ ___

PI: _____ **Date (mm/dd/yy):** ___ ___/___ ___/ ___ ___

To be completed by the patient.

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒		
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒		
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant	❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒		
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒

Please check you have answered EVERY question. Thank you.

To be completed by research nurse:

Score: _____

DERMATOLOGY LIFE QUALITY INDEX (DLQI) - INSTRUCTIONS FOR USE

The Dermatology Life Quality Index questionnaire is designed for use in adults, i.e. patients over the age of 16. It is self explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in one or two minutes.

SCORING

The scoring of each question is as follows:

Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question 7, 'prevented work or studying'	scored 3

The DLQI is calculated 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.

HOW TO INTERPRET MEANING OF DLQI SCORES

0 – 1	no effect at all on patient's life
2 – 5	small effect on patient's life
6 – 10	moderate effect on patient's life
11 – 20	very large effect on patient's life
21 – 30	extremely large effect on patient's life

REFERENCES

Finlay AY and Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19:**210-216.

Basra MK, Fenech R, Gatt RM, Salek MS and Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008; **159:**997-1035.

Hongbo Y, Thomas CL, Harrison MA, Salek MS and Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? *J Invest Dermatol* 2005; **125:**659-64.

Appendix J – Skin Care Instructions

Patient Instructions

Please apply the cream you were assigned at least twice a day, every day. Please start using the cream on the day you start radiation, and continue its use until you return for follow-up approximately 1 month after your last radiation treatment.

Other Considerations:

- Wear loose, comfortable cotton clothing in the area being treated.
- Avoid temperature extremes and use lukewarm water to wash.
- Do not use hot or ice packs, blade razor on irritated skin.
- Do not expose to the sun, rub or scratch irritated skin, patients may apply cool moist washers if skin feels itchy or hot.
- Pat skin dry with a soft towel after washing or air dry.
- Do not use any tapes, band aids, or dressing unless advised by clinicians.
- Do not use other topical preparations in the treatment area.
- Rinse off immediately in fresh water if swimming in a pool or salt water (if the skin is intact)

Skin Care during Radiation Therapy

ALL MOISTURIZERS MUST BE APPROVED BY YOUR NURSE:

Apply moisturizer at least twice daily. Start using within the first week of your radiation therapy.

***IMPORTANT: Do not** apply the moisturizer within four hours before your daily radiation treatment appointment.

Examples of good moisturizers that do not interfere with the radiation:

- Aveeno Skin Relief lotion, fragrance-free
- Eucerin
- Lubriderm
- Calendula cream or gel
- Aloe Vera gels
- Cetaphil
- CeraVe
- Petroleum based with mineral oil ointments:
  Aquaphor, Balmex, Elta

Soaps:
Use a gentle soap for bathing/showering such as Dove or Cetaphil.

Deodorants:
You may use regular strength deodorant/anti-perspirant such as:
Dove
Secret

Appendix K – Mandatory STRC SAE Reporting Guidelines

Data and Safety Monitoring Committee (DSMC) Serious Adverse Event (SAE) Notification SOP	Date: 02/11/2021

Mandatory DSMC SAE Reporting Requirements in WISER

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Data and Safety Monitoring Committee (DSMC).** A trial is considered a **WFBCCC Investigator Initiated interventional trial** if the following criteria are met:

1) The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
2) WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
3) The trial is designated as "Interventional" using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation. (https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

1) Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites.** These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2) Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites.

There are three types of trials that are included in this category:

a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the DSMC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either 1) **unexpected grade 4,** 2) **unplanned inpatient hospitalization ≥ 24 hours (regardless of grade)**, or **grade 5 (death)** must be reported to the DSMC using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the DSMC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the DSMC clinical member to obtain all details of the SAE, as well as all associated toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire DSMC will be generated.

THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of attribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the DSMC.

What is considered during protocol intervention?
During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

What is considered as an Unexpected Grade 4 event?
Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to DSMC.

DSMC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:

1. Make a phone call (or speak in person) to the appropriate clinical member of the DSMC according to the schedule as listed below (page if necessary).
2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console in WISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the DSMC members will not be notified until a date is entered into the DSMC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., PI, study team members and DSMC members) will be notified; remember to file a copy of the

confirmation.

3. Document that the appropriate person(s) on the DSMC has been contacted. Indicate the name of the DSMC clinician that was contacted and the date and time contacted in the Event Narrative field in the SAE console of the particular subject.
4. Document whether or not the protocol should be suspended based on the discussion with the DSMC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.
5. Follow up/update the clinical member(s) of DSMC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the DSMC clinician who was notified and Date/Time notified. In addition, state attribution by DSMC clinician as either "Unrelated", "Unlikely", "Possibly", "Probably", or "Definitely". Always include the following here:
    i. DSMC clinician name, date/time contacted and comments
    ii. Date of last dose before the event
    iii. Is suspension of the protocol needed? Y/N
7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with DSMC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N
12. SAE Classification ***This is required in order for the email notification to be sent***
13. Adverse Event Details – Enter all details for each AE associated with the SAE.
    a. Course start date
    b. Category
    c. AE Detail
    d. Comments
    e. Grade/Severity
    f. Unexpected Y/N
    g. DLT Y/N
    h. Attributions
    i. Action
    j. Therapy
    k. Click ADD to attach the AE Detail to the SAE.
14. Enter Date Notified DSMC -- ***This is required for the email notification to be sent***
15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do

not receive an email within 5 minutes, check that you have entered the "Date Notified DSMC" and the "SAE Classification". If these have been entered and the email still has not been received, take a screen shot of the SAE in WISER and immediately email it out to all of the DSMC members listed in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the DSMC members immediately so that their assessment can be obtained within the 24 hour period requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

The Clinical Members of DSMC to Notify by Phone or Page:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser
Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes
Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman
Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed
Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu
Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars

Glenn Lesser, MD – Hematology Oncology

Mercedes Porosnicu, MD-- Hematology Oncology

Ryan Hughes, MD – Radiation Oncology
Michael Goodman, MD -- Hematology Oncology
Daniel Reed, MD -- Hematology Oncology
Mary Beth Seegars, MD -- Hematology Oncology

Definition of Unavailable: As a general guideline if the first clinician that is contacted does not respond to the phone call or page within 30 minutes, then initiate contact with the next DSMC clinician listed in the table above on the particular day the SAE is being reported. Allow up to 30 minutes for the new DSMC clinician to respond to a phone call or page before contacting the next member in the table. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the DSMC notification form. It is important to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of DSMC.

DSMC CLINICAN RESPONSIBILITY:

It is the responsibility of the DSMC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of DSMC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. DSMC reserves the right to disagree with the Investigator's assessment. If DSMC does not agree with the Investigator, DSMC reserves the right to suspend the trial pending further investigation. If there is any immediate danger or harm that could be present for a future patient based on the information provided in the DSMC report then an immediate

suspension of enrollment shouldbe considered.

AMENDMENTS TO PREVIOUS REPORTS

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the DSMC and using that email "reply to all". Entitle this new email "**Amendment** for (list date of event and patient ID)" this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click Update. This will allow additional information to be added.

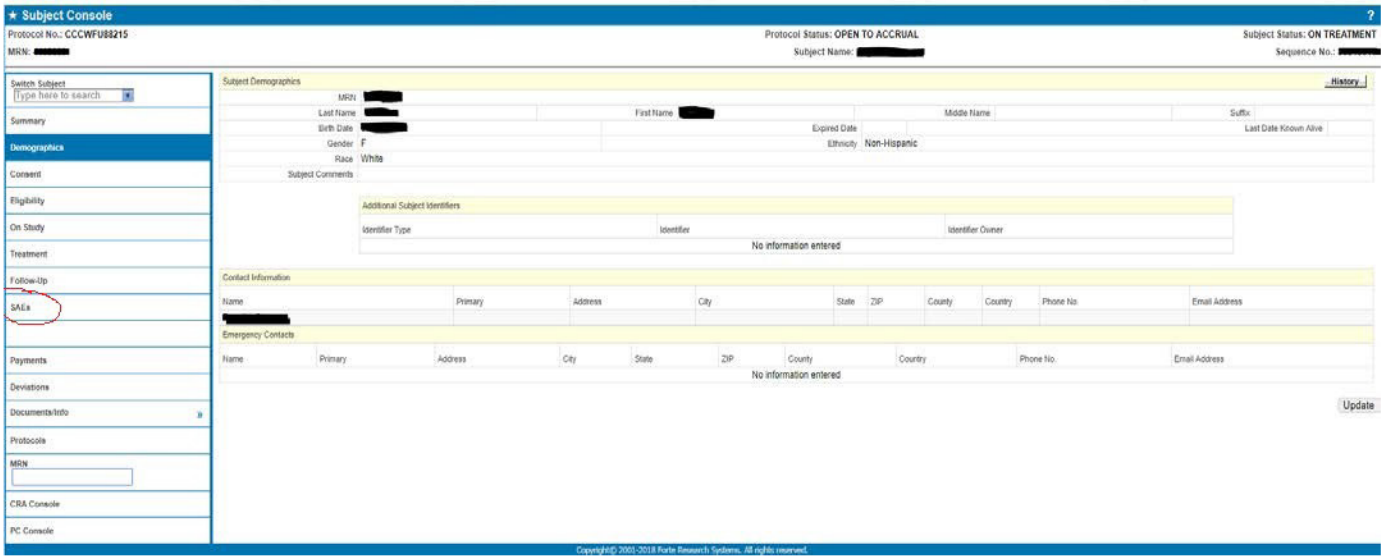
Acronyms

AE – Adverse Event
DSMC-Data and Safety Monitoring Committee
SAE-Serious Adverse Event
WFBCCC – Wake Forest Baptist Comprehensive Cancer Center
NCI-National Cancer Institute
WISER –Wake Integrated Solution for Enterprise Research

Screen Shots:

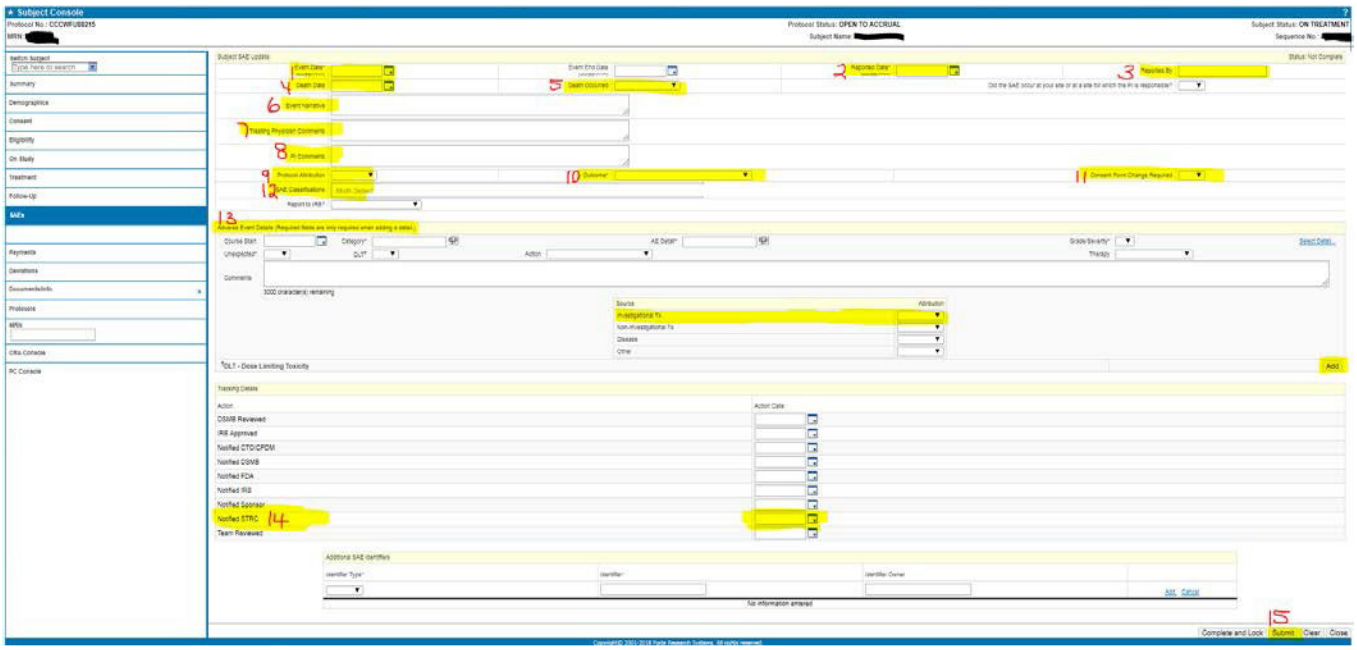
The following screen shots come from the SAE Console within the Subject Console in WISER.

Screen Shot 1:

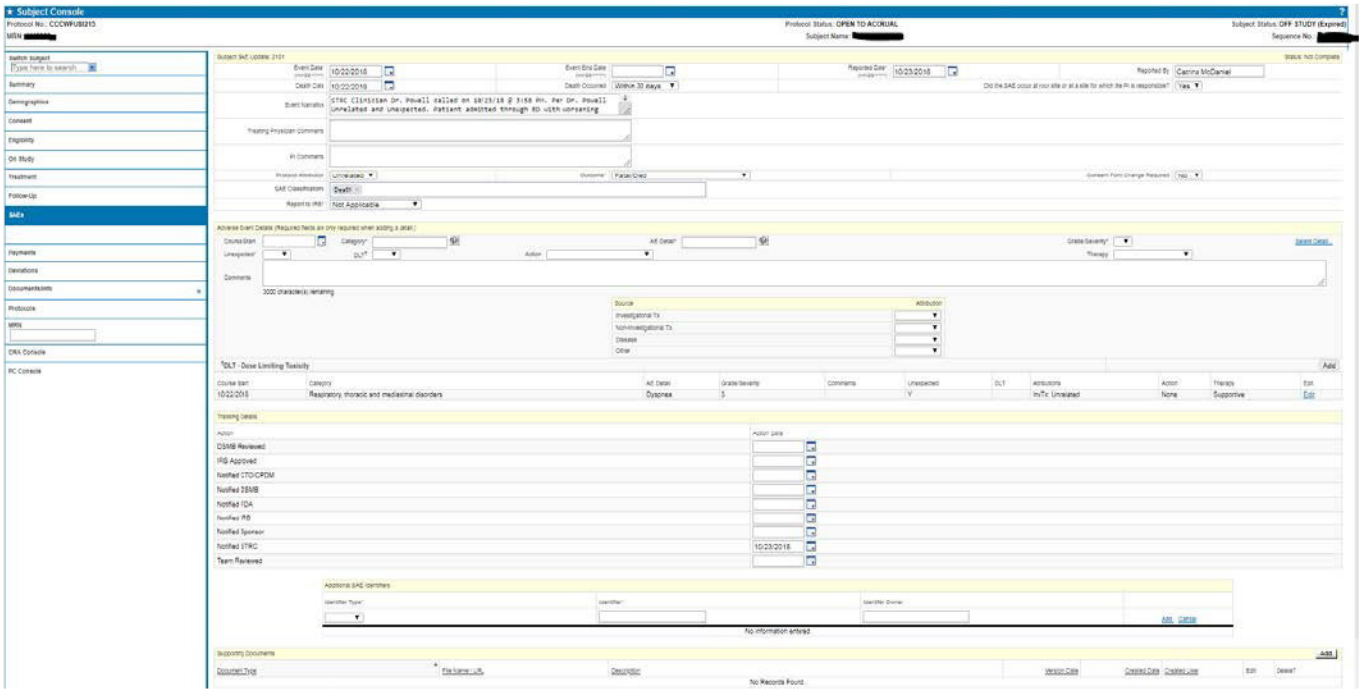


Screen Shot 2:

Screen Shot 3:



Screen Shot 4:



Appendix L - Adverse Event Log

WFBCCC Adverse Event (AE) Log*

*Due to the nature of this pilot feasibility study, the only adverse event collected will include unexpected dermatological events during and within 1 month after the completion of RT.

PI: _____ **Subject PID:** _____ **MRN:** _____

Cycle #: _____ **Cycle Start Date:** _____ **Cycle Start Time:** _____ **Cycle End Date:** _____ **Cycle End Time:** _____

Adverse Event CTCAE Term	**Lab Value**	**Grade** (1-5) per CTC	**Start Date**	**End Date**	**Attribution** DEF= Definite PROB= Probable POSS= Possible UNLK= Unlikely UNRL= Unrelated	**Expected** N=No Y=Yes	**Serious Adverse Event Detail** NO=No LT=Life Threatening DTH=Death DIS=Disability HOS=Hospitalization CA=Caused congenital anomaly RI=Required intervention to prevent impairment	**Dose Limiting Toxitity (DLT)** N=No Y=Yes	**Action Taken** NO=None DR=Dose Reduced RI=Regimen Interrupted TD=Therapy discontinued INTR=Interrupted then reduced	**Therapy Given** NO=None SYM=Symptomatic SUP= Supportive VSUP=Vigorous supportive	**Reportable?** IRB- IRB STRC- STRC FDA- FDA SPON- Sponsor (Mark all that apply)	**Adverse Event Report (AER) Filed** N=No Y=Yes	**Outcome** R= Recovered TX=Still under treatment/ observation A=Alive with sequalae D=Died	**Treating MD Initials/Date**

Serious Adverse Event: Hospitalization; Disability; Birth Defect; Life-threatening; Death.

CTCAE Version 5 - https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

STRC- Safety and Toxicity Review Committee | Version 1/10/18

Appendix M – 30 Day Treatment Follow-up Form

Study Number: ___ ___ ___ ___ ___	**PID:** ___ ___ ___ ___ ___ ___ ___ ___ ___
PI: _____	**Date (mm/dd/yy):** ___ ___/___ ___/ ___ ___

Instructions: Fill out this form post washout to assess Adverse Events

Name of person completing form _____

Did the subject have any adverse events? If yes, document on AE log (**Note*: If a SAE occurs in this period, report the event as required per protocol**)

- ☐ Yes
- ☐ No

Was the subject removed from the study? If yes, document on off study form

- ☐ Yes
- ☐ No

Did the subject withdraw from the study? If yes, document on the off treatment form

- ☐ Yes
- ☐ No

Did the subject complete the study? If yes, document on the off study form

- ☐ Yes
- ☐ No

Comment:

_____
_____
_____
_____

Appendix N – Off-Study Form

Study Number: ___ ___ ___ ___ ___	**PID:** ___ ___ ___ ___ ___ ___ ___ ___ ___
PI: _____	**Date (mm/dd/yy):** ___ ___/___ ___/ ___ ___

Instructions:

Off Study:

Off Study Date: __/__/____

Off Study Reason:

- ☐ Adverse Event/Side Effects/Complications
- ☐ Death (if death fill out Survival Form)
- ☐ Enrolling Physician Decision
- ☐ Patient lost to follow-up; Date of last contact (mm/dd/yy): __ __/__ __/__ __
- ☐ Patient refused follow-up
- ☐ Protocol-defined follow-up completed
- ☐ Other

Explain:

_____
_____
_____
_____

Off Treatment Form

Study Number: ___ ___ ___ ___ ___	**PID:** ___ ___ ___ ___ ___ ___ ___ ___ ___
PI: _____	**Date (mm/dd/yy):** ___ ___/___ ___/ ___ ___

Instructions:

Off Treatment:

1. Off Treatment Date: __/__/____

2. Off Treatment Reason:
   - ☐ Adverse Event/Side Effects/Complications
   - ☐ Alternative Therapy
   - ☐ Cytogenetic resistance
   - ☐ Death on Study
   - ☐ Disease progression before active treatment
   - ☐ Disease progression, relapse before active treatment
   - ☐ Enrolling Physician Decision
   - ☐ Lost to follow-up
   - ☐ No treatment, per protocol criteria
   - ☐ Patient off treatment for other complicating disease
   - ☐ Patient withdrawal or refusal after beginning protocol therapy
   - ☐ Patient withdrawal or refusal prior to beginning protocol therapy
   - ☐ Treatment completed per protocol criteria
   - ☐ Other

3. Explain:

_____
_____
_____
_____

Appendix O - Survival Form

Study Number: ___ ___ ___ ___ ___	**PID:** ___ ___ ___ ___ ___ ___ ___ ___ ___
PI: _____	**Date (mm/dd/yy):** ___ ___/___ ___/ ___ ___

Instructions:

1. Last known Survival Status:
   - ☐ Alive
   - ☐ Dead
   - ☐ Lost to Follow-up
2. Expired Date: __/__/____
3. Last known Alive Date: __/__/____
4. Survival Status source: _____
   Instructions: Source can be EMR, obituary, family member etc. Add to comments in wiser follow-up section
5. Comment:

_____
_____
_____
_____

Appendix P - Withdrawal of consent for the intervention and medical record use

Study Number: ___ ___ ___ ___ ___	**PID:** ___ ___ ___ ___ ___ ___ ___ ___ ___
PI: _____	**Date (mm/dd/yy):** ___ ___/___ ___/ ___ ___

Instructions:

- I withdraw consent for further study intervention/treatment.

  ☐Yes ☐No Initials: _____

- I withdraw from further research activities (surveys, questionnaires, research assessments and other non-invasive research activities).

  ☐Yes ☐No Initials: _____

- I withdraw my consent to allow the further collection of research-related information from my medical record to be used in this research project.

  ☐Yes ☐No Initials: _____

Specimen collection/use withdrawal (no research specimen collection, skip section)

I withdraw my consent for any use of my specimen for this current research.

☐Yes ☐ No Initials: _____

I withdraw my consent for any use of my specimen for future research.

☐Yes ☐No Initials: _____

I acknowledge that any data or de-identified materials that have already been created from my specimen may still be used for research. Initials: _____

Patient signature: _____

Date (mm/dd/yy): ___ ___/___ ___/___ ___

Investigator signature: _____

Date (mm/dd/yy): ___ ___/___ ___/___ ___

Comments:
_____
_____
_____
_____
_____
_____
_____