PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR

R. Rox Anderson, MD

PROTOCOL TITLE

Treatment of Field Cancerization for Reduction in Tumor Burden – A Prospective Study

NCT NUMBER

NCT02150863

FUNDING

Wellman Center for Photomedicine

VERSION DATE

December 28, 2016

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

This project aims to treat field cancerization in a manner that will reduce the tumor burden in patients with significant photodamage

1. To demonstrate that we can reduce the non melanoma skin tumor burden over time by treating the entire field of actinic keratoses and atypical keratinocytes.
2. To compare the efficacy and side effects of ablative CO2 laser resurfacing vs. ablative CO2 laser resurfacing plus post treatment suction blister epidermal grafts vs. control (no intervention).
3. To demonstrate a reduction in the number of actinic keratosis over time
4. To demonstrate an improvement in clinical appearance of the treatment area
5. To demonstrate a reduction in the degree of P53 mutations seen with histopathology
6. To demonstrate that subjects tolerate the treatment with few side effects
7. To demonstrate increased telomere length in treated areas

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Field cancerization is a risk for any individual with excessive and prolonged sun exposure, immunosuppression, or exposure to radiation or carcinogens. We are very good at treating the skin cancer but if we leave behind the atypical field of keratinocytes it is only a matter of time

until the next skin cancer needs to be excised. The current treatment regimensfor treating AKs and SCCs involve frequent office visits with extensive cryotherapy, numerous biopsies and excisions.We often use topical medications to treat field cancerization, such a 5-fluorouracil or imiquimod. These treatments are often ineffective and need to be repeated frequently. The need for multiple treatments may be related to compliance. Often people cannot tolerate these treatment regimens. Thus there is the need for an optimized treatment regimen to improve clearing the field of atypia and precancerous lesions. This would cut down on cost, risks of surgical procedures, and patient discomfort.

We want to evaluate of effectiveness of ablative carbon dioxide (CO2) laser used to precisely remove the epidermis of an entire field, thus removing all the typical keratinocytes and basal stem cells that have been mutated. After the CO2 treatment a portion of the area treated would then be covered with autologous epidermal skin grafts from a non-exposed area (buttocks or thigh). We hypothesize that the epidermal skin grafts would not only improve/hasten the wound healing process after CO2 but it would also provide the field with stem cells that have yet to receive damaging radiation.

Ablative CO2 laser was first used by surgeons to cut and vaporize tissue. It then became a popular device with both surgeons and dermatologists for treatment of deep facial rhytides. More recently these lasers have been used to treat significantly photodamaged skin and actinic keratoses. The studies showing varying rates of reduced AK counts over short periods of time. The longest follow up being 2 years.

Suction blister autologous epidermal grafting is a simple procedure being used most commonly for vitiligo, but also wound healing and scarring. There are several IRB approved protocols at MGH already using this technique (PI: Alexandra Boer Kimball, MD, MPH).

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

The proposed pilot study is a 3 year prospective, randomized, controlled comparison of a single treatment with carbon dioxide laser resurfacing vs. carbon dioxide resurfacing plus autologous epidermal skin graft from a non sun exposed site vs. control. Thirty subjects will receive treatment with each of the modalities on randomly-assigned portions of the treatment area. The primary measures of efficacy are (a) count of the number of actinic keratosis and non melanoma skin cancers, (b) blinded evaluation of severity from standard digital photographs taken before and after the treatments, and (c) change in histology before and after treatment: seen by grading and change of p53 immunostaining. Other study endpoints include time point to the next skin cancer is found in the treatment area, overall clinical appearance, change in mutant P53 of skin samples, and telomere length variability.
Safety measures include (a) pain, (b) scarring, (c) wound healing, (d) and infection

Subjects will be recruited through advertisements posted within the hospital(s), outpatient dermatology clinics and partners electronic mail.

Inclusion criteria

1. Subjects with ages between 18 and 85 years, male or female.
2. Subjects with at least 4 clinically diagnosed AKs per treatment site (up to 200 sq cm), excluding the face.
3. Subjects with history of at least 1 skin cancer within the past year
4. Willingness to participate in the study
5. Informed consent agreement signed by the subject
6. Willingness to follow the treatment schedule and post treatment care requirements
7. Willingness to not use topical or systemic (oral) TREATMENT medications including imiquimod, 5 Fluorouracil, photodynamic therapy, during the treatment period.
8. Has not had treatment for AKs in the treatment area for 4 weeks prior to enrollment

Exclusion criteria

1. Subjects with active skin cancer in the treatment area. Once the non-melanoma skin cancer has been treated, the subject can be immediately enrolled.
2. Infection of the area to be treated
3. An open wound in the area to be treated
4. Presence of suntan in the area to be treated, or active tanning during the study
5. Subjects who have taken medication known to induce photosensitivity in the previous 3 months
6. The patient has any contraindication to use of the CO2 laser
7. Subject is unable to comply with treatment, home care or follow-up visits
8. Subject is pregnant or breast feeding
9. Prior use of topical retinoids, 5 fluorouracil, or imiquimod in treated areas within one month of initial treatment
10. Prior skin treatment with laser or other devices in the treated area within two months of initial treatment or during the course of the study;
11. Adverse reactions to compounds of any external agent (e.g., gels, lotions or anesthetic creams) required for use in the study, if no alternative to the said agent exists;
12. Concurrent inflammatory skin conditions, including, but not limited to, eczema, contact dermatitis of any severity;
13. Active Herpes Simplex at the time of treatment;
14. Multiple dysplastic nevi in area to be treated;
15. Having a bleeding disorder or taking anticoagulation medications, including heavy use of aspirin, in a manner which does not allow for a minimum 10 day washout period prior to each treatment (as per the patient's physician discretion);
16. Significant concurrent illness, such as uncontrolled diabetes, (i.e., any disease state that in the opinion of the Investigator would interfere with the anesthesia, treatment, or healing process);
17. Mentally incompetent, prisoner or evidence of active substance or alcohol abuse;
18. Any condition which, in the Investigator's opinion, would make it unsafe (for the subject or study personnel) to treat the subject as part of this research study.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

This study will be conducted at the Wellman Center for Photomedicine human studies facility at MGH. The first contact will be made in by the subject in response to the study advertisement. During this first study contact subjects will be informed regarding the goals of the study, inclusion/exclusion criteria, study procedure, potential benefits, risks and duration of the study. Subjects will be asked if they would like a copy of the consent form to read, either through the mail or email. Subjects who meet the inclusion and exclusion criteria and remain interested in the study will be in invited for a screening visit.
The study involves 1 screening visit, 1 baseline/ treatment visit, and 10 study visits over a period of 3 years. Objective and safety assessments will be done at all treatment visits.

Visit	Informed consent	Urine preg test	TX	Photo	# NMSC prior	AK/NMSC count	Biopsy	Overall Appearance scale	AE	Pain scale (VAS)	Patient side effect report	Inv wound assess
Screen	X											
Baseline/TX (Day 0)		X	X	X	X	X	X	X	X	X		
Day 3				X				X	X	X	X	X
Day 7				X				X	X	X	X	X
Week 4				X		X		X	X	X	X	X
3 month				X		X	X	X	X			X
6 month				X		X		X	X			
1 year				X		X		X	X			
1.5 – 2.5 year visits				X		X			X			
3 year				X		X	X	X	X			

Baseline/Treatment Visit 1(Day 0)

- **Baseline and treatment can occur on separate days if necessary. These visits will occur within 2 weeks of each other if done separately**

Part I– Baseline Evaluations (lasting 1 hour).

Part II- Treatment (lasting 2.5 hours)

Part I– Baseline Evaluations (lasting 1 hour).

The investigator will determine the treatment area

I. **AK count within the treatment area**
II. **Confirm no clinically evident NMSC within the treatment area**
III. **Obtain history of number of skin cancers and locations. History will be taken orally from patient but will also review the medical records.**
IV. **Tracings of the treatment area and control site as needed to document**

V. Shave biopsy technique will be used to harvest epidermal biopsies for histologic assessment. 6 scouting biopsies will be done in the treatment area for histologic evaluation and immunostaining

VI. Baseline pre-treatment Photography of treatment area and control site

Shave biopsy for histology

Area will be prepped with alcohol swab, injected with Lidocaine 1% with or without epinephrine. Shave biopsy will be performed with a dermablade. Tissue samples will be taken to the lab and processed for immunostaining of p53 and PCR to determine telomere length. A portion will be frozen and backed for PCR analysis at the end of the study.

Part II- Treatment (lasting 2.5 hours)

I) Urine pregnancy test for female not yet in menopause
II) Subject will receive laser treatment to the treatment area. Topical anesthesia will be applied for 1 hour prior to the laser treatment.
III) Epidermal suction blister graft harvest from donor site and application on randomized treatment area
IV) Adverse event evaluation
V) Patient assessments: pain

Procedures in more detail

Laser treatment

The laser used is the Ultrapulse CO2 Laser (Lumenis). Patients will be treated according to the standard of care. The settings used for the CO2 laser will be commonly used settings that will ablate down to the bottom layer of the epidermis (8 – 20 J/cm2). Any remaining epidermis will be removed with saline soaked gauze. The papillary dermis has a characteristic glistening appearance and this will also be used as a treatment endpoint. If the papillary dermis is seen, the treatment in that area will be considered completed.
Participants or caregivers will be instructed to do saline soaked gauze soaks three times daily and apply Vaseline™ or Aquaphor™ onto the treated areas for up to 7 days post op as needed. Wound care instructions will be given to the patient, and a Day 3 follow-up visit will be scheduled.

Epidermal Blistering and Micrograft Preparation

A suction device will be applied to area of skin approximately 5.0 cm in diameter. This will be left in place approximately 30-40 minutes and may cause mild discomfort because of the suction. After the microblisters have been raised, the blister roofs (a superficial epidermal sample) with an average thickness of 200 microns and size of 1.75 mm in diameter will be removed and transferred to a sterile Tegaderm wound dressing that will be applied to the recipient site. The superficial donor wound will then covered with sterile Tegaderm or Duoderm.

Post- Procedure follow up Visits (Day 3, Day 7) (lasting 30 minutes)

I) Photography

II) Exam of the treatment area: wound check; evidence of scarring, evidence of infection; evidence of healing
III) Adverse event evaluation
IV) Investigator assessments: wound assessment, overall clinical appearance
V) Patient assessments: pain scale and side effects

Follow-up Visits(Week 4) (lasting 30 minutes)

I) Photography
II) Exam of the treatment area: AK count, evaluate for clinically appearing NMSC present; evidence of scarring, evidence of infection; evidence of healing. Also will get history from patient: visits to dermatologist? and treatments rendered?.
III) Adverse event evaluation
IV) Investigator assessments: wound assessment, overall clinical appearance
V) Patient assessments: Pain scale and side effects

Follow-up Visits
(Month 3) (lasting 1.5 hours)

I) Photography
II) Exam of the treatment area: AK count, evaluate for clinically appearing NMSC present; evidence of scarring, evidence of infection; evidence of healing . Also will get history from patient: visits to dermatologist? and treatments rendered? Will also review medical records to confirm the history.
III) 6 scouting epidermal biopsies, using shave biopsy technique (from the treatment area) for histology and immunostaining. Will also bank a portion for PCR at the end of the study.
IV) Adverse event evaluation
V) Investigator assessments: wound assessment, overall clinical appearance

Follow-up Visits(6 months, 1 year, 1.5 year, 2 year, 2.5 year) (lasting 30 minutes each)

I) Photography
II) Exam of the treatment area: AK count, evaluate for clinically appearing NMSC present; evidence of scarring, evidence of infection; evidence of healing . Also will get history from patient: visits to dermatologist? and treatments rendered? Will also review medical records to confirm the history.
III) Adverse event evaluation
IV) Investigator assessments: overall clinical appearance

End of Study visit (3 year) (lasting 1.5 hours)
Patients will exit the study after 3 years
II) Photography
III) Exam of the treatment area: AK count, evaluate for clinically appearing NMSC present; evidence of scarring, evidence of infection; evidence of healing . Also will get history from patient: visits to dermatologist? and treatments rendered? Will also review medical records to confirm the history

IV) **6 scouting epidermal biopsies, using shave biopsy technique (from the treatment area) for histology and immunostaining. Will also bank a portion for PCR at the end of the study.
V) Adverse event evaluation
VI) Investigator assessments: overall clinical appearance

** During the course of the study, the subjects will have a total of 18 scouting epidermal biopsies using the shave biopsy technique

Evaluation of Safety and Efficacy
Assessed by investigators (non-blinded) and by blinded evaluators (clinical photographs), periodically for 3 years after a single treatment session.

Reported by the Patients
Specific form is attached.

I. Side effects reported by the patient:

To assess major and minor side-effects, patients will be asked for each treatment site to fill in the following sentence for each test site: "**The side effects I experienced after the treatment were:**" E.G.

Table I. **N/A**: Did not have this side effect / **1:** Mild / **2:** Moderate / **3:** Severe

A. Blistering	N/A	1	2	3
B. Scarring	N/A	1	2	3
---	---	---	---	---
1. Swelling	N/A	1	2	3
2. Redness	N/A	1	2	3
3. Scabs (crusting)	N/A	1	2	3
4. Weeping skin (pustulation)	N/A	1	2	3
5. Scaling or flaking skin (exfoliation)	N/A	1	2	3
6. Itchy skin	N/A	1	2	3
7. Erosion (ulceration)	N/A	1	2	3
8. Tanning	N/A	1	2	3
9. Lightening of the skin	N/A	1	2	3
11. Wheals	N/A	1	2	3
12. Bleeding	N/A	1	2	3
13. Folliculitis/ Acne	N/A	1	2	3
14. Oozing	N/A	1	2	3
15. Change in sensitivity/numbness	N/A	1	2	3

I. Pain assessment - Visual Analog Scale (VAS).

The VAS will be completed by study subjectimmediately after the treatment, and at each procedure follow up visit (Day 3, Day 7, week 4)

Pain is any of the following: sensation of tingling, stinging, prickling, or burning feeling, heat under the skin, tenderness, mild, moderate or severe pain).

Specific VAS form is attached

Patients will be asked to circle the number below that most closely corresponds to pain associated with their DISEASE.

□ □ □ □ □ □ □ □ □ □ □

0 1 2 3 4 5 6 7 8 9 10

(NO PAIN WORST PAIN)

Reported by the Investigators and Blinded-evaluators

Reported by the Investigator

Specific form is attached.

Investigator's Wound Assessment

Table 2. **N/A**: Did not have this side effect / **1:** Mild / **2:** Moderate / **3:** Severe

A. Blistering	N/A	1	2	3
B. Scarring	N/A	1	2	3
---	---	---	---	---
1. Swelling	N/A	1	2	3
2. Redness	N/A	1	2	3
3.Crusting	N/A	1	2	3
4.Pustulation	N/A	1	2	3
5. Scaling or flaking skin (exfoliation)	N/A	1	2	3
6. Erosion (ulceration)	N/A	1	2	3
7.Hyperpigmentation	N/A	1	2	3
9.Hypopigmentation	N/A	1	2	3
10.Urticaria	N/A	1	2	3
11.Infection	N/A	1	2	3
12. Folliculitis/ Acne	N/A	1	2	3
14. Oozing	N/A	1	2	3

Overall Appearance Scale (blinded MD to complete with photos)

- Physicians will consider both cosmetic appearance but also the degree of photodamage and clinical atypia.

	Co2 treatment site	**Co2 + epidermal graft Treatment site**	**Control site**
Excellent	□ 5	□ 5	□
Good	□ 4	□ 4	□
Satisfactory	□ 3	□ 3	□
Poor	□ 2	□ 2	□
Unacceptable	□ 1	□ 1	□

End points:

- AK count
- NMSC count
- change in overall clinical appearance
- time to healing
- change in p53mutations
-change in telomere length

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

Field cancerization and pre-skin cancers are currently treated through a number of ways including: spot treatment with cryotherapy, biopsy, excision; photodynamic therapy; or topical therapies, such a 5-fluorouracil, imiquimod, or ingenolmebutate. These treatments are often ineffective and need to be repeated frequently. The CO2 laser is another method for destruction of the epidermis. The hope is that this in office treatment would be effective as a single treatment. In addition, in office CO2 would be better controlled than at home treatments with topical creams or the spot treatment approach with cryotherapy, biopsy, or excision.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

The CO2 laser has been used for many years and the standard of care for use is well established. All standard of care laser safety procedures will be followed (i.e. wearing appropriate eye protection) and all standard of care measures for prepping for a clean field will be taken minimize risk of infection. Will also review wound care instruction with patients and give them written instructions to take home.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

There is only one treatment for this procotol. Safety data will be collected at each visit of the study. We will ensure that the patients continue to have regular dermatologic care. This study will not interfere with treatment of future skin conditions.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

Foreseeable Risks and Discomforts of Ablative CO2 laser

	Common	Uncommon
Major:		
1. Severe Pain (Pain 8/10 or higher on VAS scale)		x
2. Blistering (with potential for secondary infection)		x
3. Ulceration (deep erosion, deep wound) with scarring		x
4.Blindess (There is a risk of blindness from the CO2		X

laser. Everyone in the room will wear protective goggles or corneal shields at all times during the treatment to prevent eye injury.)		
Minor:		
1. Mild to Moderate Pain (Pain 1-7/10 on VAS scale) (tenderness) (tingling, stinging, prickling, or burning feeling, tenderness) Topical anesthesia plus cooling air (Zimmer) will decrease pain during treatment. During the treatment we will be asking the patient to rate their level of pain according to the visual analog pain scale that will be provided and explained to them. If at any time during the procedure the patient indicates a pain level of 7 or above based on the visual analog pain scale laser treatments will stop and use intralesional 1% lidocaine for anesthesia in the treatment area	x	
2. Swelling (edema)	x	
3. Redness (erythema)	x	
4. Crusting (scabbing)	x	
5. Pustulation (weeping skin)	x	
6. Exfoliation (scaling or flaking skin)	x	
7. Itchy Skin	x	
8. Ulceration (erosion)	x	
9. Tanning (pigmentation)< 3 months	x	
10. DISEASE flare		X
11. Hypopigmentation (lightening of the skin)	X	
12. Minor Blistering (vesiculation)		x
13. Wheals		x
14. Bleeding	X	
15. Folliculitis/ acne		x
16. Oozing	X	
17. Dysesthesia (change in sensitivity, numbness)		x
18. Infection: The area may become infected; however, keeping the site clean and using the petroleum ointment should prevent this. If the site does become infected, the patient may need to take oral antibiotics. Signs of infection include redness or swelling lasting longer than 3 days, oozing, or fever. If the patients experience any of		X

these symptoms, they will be instructed to contact the study doctor for immediate evaluation. Oral valacyclovir and dicloxacillin will be given to the patients to prevent the risk of herpes virus related complications.		
19. Milia		X

CO2 ablative laser – Complications: All are uncommon and include pain lasting greater than 7 days, scarring, bleeding, hyper/hypopigmenation, secondary infection
There are rare reports blindness from complication/malfunction of the UltraPulse Co2 device when used without proper eye wear. The patient and all those in the room will wear appropriate eyewear for the entire visit.

Foreseeable Risks and Discomforts of Skin Biopsy

Skin Biopsy – Risks and discomforts

	Common	Uncommon
Pain	X	
Edema (swelling)	X	
Erythema (redness)	X	
Crusting (scabbing)	X	
Tenderness	X	
Itching	X	
Small scar	X	
Bruising	X	
Bleeding	X	
Skin discoloration (hyperpigmentation or hypopigmentation)	X	

Biopsy complications: All very rare: prolonged pain > 7 days, ulceration, oozing, infection, dysesthesia, bleeding

Suction blister epidermal skin grafts– Risks and discomforts

	Common	Uncommon
Pain		X
Edema (swelling)		X

Erythema (redness)	X	
Crusting (scabbing)	X	
Tenderness, Burning sensation		X
Itching	X	
Small scar		X
Bruising		X
Bleeding		X
Skin discoloration (hyperpigmentation or hypopigmentation)	X	
Infection		X

Psychosocial (non-medical) risks

Side-effects related to the treatment may affect patient's social life, especially within those concerned with physical appearance. Covering the treated areas or missing work/school for 1-7 days after the treatment is be advised to subjects

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

Participating patients may have a decrease in the number of future actinic keratosis and non melanoma skin cancers within the treatment area. Potentially they will need less future treatment with cryotherapy, surgical excisions, topical chemotherapy, etc.

Potential benefits to society

If this treatment regimen does decrease the number of future actinic keratosis and non melanoma skin cancers within the treatment areait will provide physicians with another treatment option. A single treatment with a CO2 laser would be much more cost effective than recurrent cryotherapy, biopsies, excisions, etc. The treatment would not only be cost effective but time efficient.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

The risks and benefits of the research are fairly distributed among the populations that stand to benefit from it. Pregnant or breast feeding women will be excluded because the use of epinephrine in the anesthesia is considered class C by the FDA. In addition, lasers are typically not used in a pregnancy patient. Children will be excluded but it is very unlikely that children develop field cancerization, pre skin cancers, or full blown non melanoma skin cancers. No other group of persons will be categorically excluded from the research.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

Individuals who do not speak English will not be denied participation in this research. Translation will be provided if need, with appropriate consent form.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

Subjects will be recruited through advertisements posted within the hospital(s), outpatient dermatology clinics and partners electronic mail. We feel that recruitment may be augmented if we target private dermatology practices where physicians are currently treating many patients with skin cancers. In this way we hope to tap into a pool of eligible and willing subjects. We also intend to make calls to private practices and meet with the clinicians to explain the study and post study advertisements. The first contact will be made in by the subject in response to the study advertisement. During this first study contact subjects will be informed regarding the goals of the study, inclusion/exclusion criteria, study procedure, potential benefits, risks and duration of the study. Subjects will be asked if they would like a copy of the consent form to read, either through the mail or email. Subjects who meet the inclusion and exclusion criteria and remain interested in the study will be in invited for a screening visit. During the screening visit, an investigator will ask the subject a few questions to ensure that inclusion and exclusion criteria are met, and to visually examine the area to be treated.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

The topical anesthesia and study supplies will be purchased the Wellman Center for Photomedicine to be used in this study with departmental discretionary funds. We will reimburse subjects according to the grid below for each visit that they complete. If subjects do not complete all visits, they will be compensated for the visits that they do complete. The compensation for taking part of this study will be paid at the last follow-up visit (#3). Parking vouchers for the hospital garage for all study visits will be given immediately after each study visit or follow-up visit. Clinically, all patients who finish this research may have some benefit of the treatments.

Payment Schedule per visit

Study Events		All patients Payment
Visit	Baseline Evaluations/Treatment (Day 0)	**$35**
Visit	Wound follow up Visits (Day 3, 7 and week 4)	**$20/visit ($60)**
Visit	Follow-Up Visit month 3	**$20**
Visit	Follow-Up Visits (6 months – 2.5 years)	**$20/visit ($100)**
Visit	End of study (Year 3)	**$20**
	Total	**$235**

Lunch vouchers (coupons) of $10 to pay for your meal in the hospital cafeteria for the Baseline/treatment visit

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
http://healthcare.partners.org/phsirb/recruit.htm

Guidelines for Advertisements for Recruiting Subjects
http://healthcare.partners.org/phsirb/advert.htm

Remuneration for Research Subjects
http://healthcare.partners.org/phsirb/remun.htm

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Following the investigator's determination, the Informed Consent document will be reviewed, by the investigator, with the subject and signed if the subject understands and accepts the document. With this, the subject will be enrolled in the study.
Subjects will have as much time as necessary to consult with family members or their physician before enrolling in the study. If the subject understands and accepts the document, it will be signed. The estimated time for the review and the explanation of the consent form is about 30 minutes. No treatment or other data collection will be obtained before a subject is consented. If a potential subject if found in the investigators' own clinic the patient will be notified that participation is voluntary and choosing not to participate will no have impact on his treatment in the clinic.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
http://healthcare.partners.org/phsirb/newapp.htm#Newapp

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects
http://healthcare.partners.org/phsirb/infcons.htm

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

The principal investigator and sub investigator will be responsible for the safety monitoring. Safety data will be collected at each visit of the study: adverse events, serious adverse events, side effects from treatment. The safety data will be reviewed every 3 months. SAE's will be dealt with immediately. It will be up to the investigator the develops the SAE to take immediate action. Efficacy data will be collected at each study visit. Blinded investigators will perform

overall efficacy assessments of this study. The Principal Investigator will be reviewing data on an ongoing and consistent basis throughout the duration of the study. The Principal Investigator is responsible for protecting the rights, safety, and welfare of subjects under his/her care. Principal investigator will be responsible for this review and for determining whether the research should be altered or stopped. If any severe adverse effect or death directly related to the treatment proposed occurs, Principal Investigator will report to the IRB and an expert group or an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

Any adverse events will be reviewed and analyzed by the Principal Investigator as soon as the event occurs and will be documented on Redcap. Any unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems including adverse event reporting guidelines.

Patients will receive only one study treatment (visit 0). After that, no test site will receive study treatment (follow-ups). The patients will continue to have routine dermatologic care. If a pre-skin cancer, skin cancer, or other dermatologic disease develops within the treatment area or the control it will be treated with the standard of care by either the patient's dermatologist or the investigators of this study. Our study documents will note all treatments that are needed in the treatment area and the control. We expect that the control sites will not improve as much as treated sites, and they will serve also as a comparative endpoint.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The Principal Investigator will be reviewing data on an ongoing and consistent basis throughout the duration of the study. Principal investigator will be responsible for this review and for determining whether the research should be altered or stopped. If any severe adverse effect or death directly related to the treatment proposed occurs, Principal Investigator will report to the IRB and an expert group or an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

For guidance, refer to the following Partners policies:
Data and Safety Monitoring Plans and Quality Assurance
http://healthcare.partners.org/phsirb/guidance.htm#13

Reporting Unanticipated Problems (including Adverse Events)
http://healthcare.partners.org/phsirb/guidance.htm#7

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

All source data will be organized and entered onto RedCap (www.redcap.partners.org). Any pertinent notes to file regarding the subject and their study visit will be documented by the study coordinator and kept in the applicable subject-file on RecCAP. All subjects will be assigned a study identification numberWe will pre-test/pilot test the source documents on RedCap prior to enrolling any subjects to ensure confidentiality and effectiveness. The source documents on RedCap will only be accessible to study staff by a special login/password. The surveys will be accessible by invitation only with a special login/password. RedCap documents will not be accessible to the public. There will be no bias to conducting research using RedCap because all surveys will be completed by the patient while he or she is at the study visit. We will use computers and internet at Wellman Center for Photomedicine for the completion of these documents.

This study will be performed in accordance with the Declaration of the World Assembly, 1975, Tokyo (Fed. Reg. 40, 16056, April 9, 1975) and the "Guiding Principles for Human Studies" of the Massachusetts General Hospital. These guidelines will be followed specifically with regard to the privacy and confidentiality of patient care and study records.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

N/A

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

N/A

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

N/A