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Study design, Procedures and Statistical Analysis Plan (SAP): 6/21/2017

Title: Validation of SHADE a Mobile Technology for Monitoring of Ultraviolet Exposure

Coordinating Center: Weill Cornell Medical College, Department of Dermatology
Collaborating Sponsor: YouV Labs, Inc. d/b/a Shade

IRB Protocol Version and Date: Version 3: 08/14/2018

Original, Version 1 dated June 21st, 2017

Amendment 1: 4/28/2018 – Updating the CRF to include a page for patients to document the medication they are currently taking, to change the order of documents within the CRF to assist with filing and to update the inclusion/exclusion criteria on the CRF to reflect the IRB

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Weill Cornell Medicine

LIST OF ABBREVIATIONS

AE	Adverse Event
AK	Actinic Keratosis
BT	Bluetooth low energy
CAT	Computer Adaptive Test
CFR	Code of Federal Regulations
CPD	cyclopyrimidine dimer
CRF	Case Report Form
ELISA	Enzyme Linked ImmunoSorbent Assay
IC	Informed Consent
ICF	Informed Consent Form
IRB	Institutional Review Board
IS	Immunosuppressive
LN2	Liquid nitrogen
NCI	National Cancer Institute
NIH	National Institutes of Health
PI	Principal Investigator
NMSC	Non-Melanoma Skin Cancer
PROMIS	Patient Reported Outcome Measurement Information System
SAE	Significant Adverse Event
SCC	Squamous Cell Carcinoma
SPF	Sun Protection Factor
UV	Ultraviolet Light
UVI	Ultraviolet Index
WC	Weill Cornell Medical College

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the Terms of Subcontract to Weill Cornell from the prime contract HHSN261201700005C to YouV Labs, Inc. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.
I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: George I. Varghese, M.D.

Signed: _____ Date: _____

PROTOCOL SUMMARY

Title:	Validation of shade, a wearable ultraviolet light monitor, for reduction of actinic keratosis
Summary:	The incidence of non-melanoma skin cancers, due to increased ultraviolet (UV) exposure, has increased by 300% over the past 2 decades. The innovative UV sensor, Shade, is designed to help people manage their UV exposure by quantifying their UV exposure levels through a linked smartphone application. In order to validate the effectiveness of Shade, we propose conducting a study communicating the level of UV exposure and correlating it with the development of actinic keratosis (AK), a precancerous lesion of the skin. We will recruit patients with multiple AK¿s. We will include renal transplant patients as this population develop AKs as well. We will evaluate the UV monitor's effectiveness in decreasing the number of AKs over a summer. This randomized partially blinded study will recruit 120 patients with a recent history of AKs and evaluate the incidence of new AKs after one summer. We will perform a control versus study group analysis. Half of the subjects (study group) will be randomly assigned to use the sensor along with its smartphone application, while the other half (control group) will receive standard of care treatment involving counseling to avoid sun exposure. Subjects will have regular standard of care visits with the dermatologist who will follow the number of actinic keratosis via clinical exam and photography. The primary outcome will be a statistically significant reduction by at least 25% of the cumulative number of newly occurred AK lesions between the control and the study group over one summer, counted at enrollment and follow-up. In subjects at one study site, skin DNA damage will also be assessed using cyclobutane pyrimidine dimers (CPD) levels measured by ELISA in both sun exposed (nose) and sun protected skin (buccal mucosa) in both the study and control groups. Secondary outcomes will look at clinical decreases by 25% in CPD levels after using the sensor.

SCHEMATIC OF STUDY DESIGN

1 KEY ROLES

Weill Cornell Medical College

Name	Title	Degrees	Unit	Role
George I. Varghese	Assistant Prof.	M.D.	Dermatology	Principal Investigator
Jonathan H. Zippin	Assistant Prof.-Clinical	M.D., Ph.D.	Dermatology	Protocol design, laboratory analytics
Darshana Dadhania	Assoc. Prof., Assist. Dir.	M.D., M.S.	Nephrology Rogosin Institute	Co-investigator
Melissa Platt	Physician Assistant	MMS	Dermatology	Study coordinator
Susan Koshy	Administrator	M.B.A.	Dermatology	Administrative Contact

The following physicians are associated with the study mainly with the role of recruiting appropriate subjects.
Clinical Co-Investigators

Name	Title	Degrees	Unit	Role
Meredith Anull	Associate Prof. – Research	Pharm D.	Surgery	Screen subjects
Choli Hartono		M.D.	Nephrology & Hypertension	Screen subjects
Joseph Jorizzo	Prof. – Clinical	M.D.	Dermatology	Screen subjects
Sandip Kapur	Prof.	M.D.	Surgery	Screen subjects
Jim Kim	Assistant Prof.	M.D.	Surgery	Screen subjects
John Richard Lee	Assistant Prof.	M.D.	Nephrology & Hypertension	Screen subjects
Jun Lee		M.D.	Nephrology & Hypertension	Screen subjects
Kira Minkis	Assistant Prof.	Ph.D., M.D.	Dermatology	Screen subjects
Patrice Robin Powell	Staff Associate	B.S., M.S.	Nursing	Screen subjects
David Serur		M.D.	Nephrology & Hypertension	Screen subjects

Manikkam Suthanthiram	Prof.	M.B., B.S.	Nephrology & Hypertension	Data analysis
Muthukumar Thangamani	Associate Prof.	M.D., M.B., B.S.	Nephrology & Hypertension	Screen subjects

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

The incidence of non-melanoma skin cancers (NMSC) has increased by 300% over the past 2 decades. Increasing ultraviolet (UV) exposure from the sun has been largely recognized as the primary risk factor for the development of these NMSCs. Actinic keratosis (AK) is a frequent pre-cancerous skin lesion caused by damage from ultraviolet exposure. Without treatment, 1-2% of these lesions evolve into squamous cell carcinoma (SCC)[1]. Therefore, the number of AKs reflects the effect of UV exposure and the risk for SCC. The burden of SCC is especially high in immunosupressed patients such as transplant patients who are at high risk of skin cancer because of their immunosuppressive medications. Morbidity/mortality of SCC in transplant patients can be as high as 25%[2]. Sunscreen use has been demonstrated to decrease the number of actinic keratosis from 24%-44%[3]. However, despite, counseling and protection, UV exposure can still be difficult to control due to a variety of factors including the lack of real time UV intensity monitoring, incomplete adherence to preventive measures, and misuse of sunscreen.

2.2 RATIONALE

The incidence of non-melanoma skin cancers (NMSC) has increased by 300% over the past 2 decades. Increasing ultraviolet (UV) exposure from the sun has been largely recognized as the primary risk factor for the development of these NMSCs. Actinic keratosis (AK) is a frequent pre-cancerous skin lesion caused by damage from ultraviolet exposure. Without treatment, 1-2% of these lesions evolve into squamous cell carcinoma (SCC)[1].

Therefore, the number of AKs reflects the effect of UV exposure and the risk for SCC. Transplant patients are at high risk of skin cancer because of the immunosuppressive medications required to prevent organ rejection. Morbidity/mortality of SCC in this patient population can be as high as 25%[2]. Sunscreen use has been demonstrated to decrease the number of actinic keratosis from 24%-44%[3]. However, despite, counseling and protection, UV exposure can still be difficult to assess and control due to a variety of factors including UV intensity, shade, the use of protective clothing and the amount of sunscreen used. A new innovative ultraviolet (UV) sensor, Shade, helps quantify daily UV exposure and can enable users to manage their UV exposure through alerts and self-reporting through a smartphone app. In order to validate the effectiveness of Shade, we propose conducting a study looking at amount of UV exposure and the development of actinic keratosis over a 12 month period in transplant patients with a history of AKs. The study protocol will be similar to the 2015 Chen et al. NEJM paper[4] which observed a difference between 11% and 20% between their study group (nicotinamide) and the control group (placebo) in the number of actinic keratoses at 3, 6, 9, and 12 months after randomization. In addition, we will test the effect of UV exposure on cyclobutane pyrimidine dimers (CPD). These are biological markers that are increased immediately with UV exposure in a dose dependent fashion. Measurement of CPD following the delivery of a known UV dose allows for a biological readout of UV effects. In addition, CPD levels represent an equilibrium between UV induced formation and DNA repair; therefore, they can also reflect chronic UV exposure[5]. The

control group will not wear a sensor. This choice of control group allows us to provide standard of care advice to these subjects. The behavior change in the treatment group is expected to be a result of both the decision to engage with the device, for example by putting it on and opening the App as well as due to the knowledge of personal UV exposure reported by the device. We expect to gather information on the cumulative UV exposure of all subjects by using an ELISA assay for cyclopyridimine dimers (CPD) from photoexposed skin.

References:
1. Criscione, V. D. et al. Actinic keratoses: Natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. Cancer 115, 2523-2530 (2009).
2. Zavos, G. et al. Nonmelanoma skin cancer after renal transplantation: a single-center experience in 1736 transplantations. Int. J. Dermatol. 50, 1496-1500 (2011).
3. Thompson, S. C., Jolley, D. & Marks, R. Reduction of solar keratoses by regular sunscreen use. N. Engl. J. Med. 329, 1147-1151 (1993).
4. Chen, A. C. et al. A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention. N. Engl. J. Med. 373, 1618-1626 (2015).
5. Yamaguchi,Y. et al. Cyclobutane pyrimidine dimer formation and p53 production in human skin after repeated UV irradiation. Exp. Dermatol. 17, 916-924 (2008).

2.3 Potential Risks and Benefits

2.3.1 Known Potential Risks

This is a minimal risk study. All subjects will, over the duration of the study, have one dermatology visit and skin check beyond the standard of care. Subjects in the treatment group will have additional information and interaction on their UV exposure to help them make the choice to minimize such exposure.

2.3.2 Known Potential Benefits

The incidence of non-melanoma skin cancers (NMSC) has increased by 300% over the past 2 decades. Vulnerable populations, such as transplant patients, have a 65 times higher risk for developing squamous cell carcinoma (SCC), and once diagnosed they have a far higher rate of developing metastases and higher mortality rate. Modification of UV exposure is difficult to teach because the rays are invisible, intuition about their intensity is demonstrably poor, and the ability to recollect exposure events is generally poor. In addition, a sudden medical change, such as immunosuppression following transplantation, can make some patients, especially skin types III-IV, become more susceptible to UV exposure and vulnerable due to limited knowledge of their daily UV requirement. The use of the UV sensor, Shade, is designed to help people manage their UV exposure by quantifying their UV exposure and alerting them of their levels through a smartphone app. The sensor is small, easy to use, and user friendly. Therefore, this device would provide an immediate benefit to study participants. In addition, if the study due to the use of Shade can demonstrate a 25% reduction in the levels of actinic keratosis (AK), and hence SCC risk, then we can extrapolate that the use of this device may decrease the morbidity and mortality of SCCs. In addition, by including a cohort of transplant patients, this study will help assess feasibility for groups at high-risk of SCC.

3 OBJECTIVES AND PURPOSE

This study will evaluate the safety and effectiveness of Shade for the management of UV-induced skin complications and data collected from this study will be used to support the proposed indications for use.

The purpose of this investigation is to demonstrate the safety and effectiveness of the Shade UV sensor and mobile

phone application product to reduce actinic keratosis.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This randomized partially blinded study will recruit 120 patients with a history of actinic keratosis (AK) lesions. A control versus study group analysis will be performed where 50% of the subjects will be randomly assigned (balanced by Fitzpatrick skin type, separate randomization lists will be made for type I&II and types III-VI, at time of first visit subjects will be assigned to study or control group by giving them the next assignment on the appropriate list) to use the SHADE sensor and its app (study group), while
the other 50% (control group) will receive standard of care UV ounseling(placebo). Subjects will have 3 visits. The first and last visit will be standard of care visits at 0 month (enrollment), and the conclusion
of their involvement. The second visit will be scheduled 3 months after the enrollment visit. The final visit will be scheduled be as soon as practical, but at least 3 months after isit 2 and after September 30. On arrival at each visit, study personnel will pre-screen patients to ensure that the sensor is not visible to physician prior to examination, for example by placing it in their pocket. At each follow up visit, the number of actinic keratosis on the face and hands will be counted and photographed. They will be treated as per standard of care protocol with cryotherapy or curettage. General use of field therapies will not be permitted during the trial. Any lesions suspicious of
non-melanoma or melanoma skin cancer will be photographed and biopsied as part of the standard of care algorithm. Cyclobutane pyrimidine dimers (CPD) levels will be measured by ELISA from exposed (cheek) and unexposed (buccal mucosa) skin scrapings collected at the first and
last visit. For each patient, the CPD level from exposed skin will be normalized to the sun protected CPD level measured from unexposed skin. We will compare the normalized CPD level of control versus study participants at each timepoint and their average CPD change over time.
We will then compare these levels with Shade UV measurements. Finally, patients will also answer questions in PROMIS (Patient-Reported Outcomes Measurement Information System) in the fields of anxiety, depression and ability to participate socially to gauge their attitudes toward the sensor

4.2.1 PRIMARY ENDPOINT

1. Quantify the impact of Shade on the cumulative number of new actinic keratoses developed over the study period.

4.2.2 SECONDARY ENDPOINTS

2. Quantify the impact of Shade on the cumulative number of new actinic keratoses observed at the final study visit.
3. Quantify the impact of Shade on the cumulative numbers of new cutaneous squamous cell carcinomas confirmed by histology over the study period.
4. Quantify the impact of Shade on the cumulative number of new nonmelanoma skin cancers (basal cell carcinomas, cutaneous squamous cell carcinomas) confirmed by histology over the study period.
5. Test the correlation between measured UV exposure and the number of new actinic keratoses.
6. Test the correlation between measured UV exposure and the number of new nonmelanoma skin cancers.
7. Quantify the impact of Shade on keratinocyte DNA damage approximated by the measurement of cyclobutane pyrimidine dimers by ELISA.
8. Quantify the impact of Shade on patients' quality of life assessed by PROMIS (Patient-Reported Outcomes Measurement Information System) in the fields of anxiety (Mental Health), depression (Mental Health), and Ability to Participate in Social Roles and Activities (Social health).
9. Assess sensor usage in the study patient population and compare characteristics of observant vs. non-observant and responsive vs. non-responsive patients.

10. Assess feasibility of the intervention for kidney transplant recipients through report of their rates for compliance and retention.

4.2.3 Exploratory Endpoints

None

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Participant Inclusion Criteria

1. Open to men and women of all skin types between the ages of 18-80
2. Prior history of actinic keratosis. Specifically,
    a. Was given a diagnosis of actinic keratosis in the past year and/or has had a history of 5 or more actinic keratosis in the past 5 years.
    b. If the patient has received a kidney transplant, the date of transplant should be longer than 6 months and should be currently on transplant immunosuppression therapy.
3. Has a smartphone that support Bluetooth low energy using a compatible operating system (iOS 8+ or Android 4+)
4. Able to commit to dermatology visits three times during the study period.

5.2 Participant Exclusion Criteria

1. Has received UV therapy in the past 6 months.
2. Has had field therapy (e.g., entire face or scalp) for the treatment of actinic keratosis (e.g. topical imiquimod, 5-fluorouracil, photodynamic therapy) in the past 3 months.
3. Patient's work and or their lifestyle is not compatible with wearing a UV sensor.
4. Has difficulty controlling their own UV exposure (nursing home, long term hospitalization).
5. Has a medical condition judged incompatible with the study by the enrolling physician including the presence of an ICD or an existing plan for an extended inpatient treatment.
6. Is an employee or direct relative of an employee of the investigational site or study sponsor.
7. Must have a smartphone that is compatible with the Shade app and is comfortable using a new app (the Shade app) on their smartphone.
    a. Jitterbug and the Samsung Galaxy J3 are not compatible with the app

Ongoing exclusion criteria:
If subject is not able to meet the commitment to ongoing visits or their answer to the exclusion criteria questions changes the subject will be removed from the study. If the change in status is temporary, less than three months, the decision to remove a subject from the study will be at the discretion of the PI.

5.3 Strategies for Recruitment and Retention

Recruiting will be performed mainly at Weill Cornell Medical Center which is closely affiliated with HSS and MSKCC providing additional access to patients. Dermatologists at Weill Cornell Medicine will be primary sources of referral within the department. In addition, Darshana Dadhania MD, MS, Transplant Nephrologist and Medical Director, Histocompatible Transplant Program will help recruit transplant patients from their transplant center.
Each patient regarding of study arm will receive $50 for each visit for a maximum of 3 visits. Patients in the study arm who use the device on a consistent basis (>40% of days per month with no gaps longer than seven days) will receive $20 per month for up to 12 months.
The sponsor may offer additional prize based motivations for use which will not exceed $1,000 for any single subject in a given month.

5.4 Participant Withdrawal or Termination

Participants may withdraw for any reason during the study.

5.4.1 Reasons for Withdrawal or Termination

Participants who can not comply with the requirement for quarterly visits will be dropped from the study.

5.4.2 Handling of Participant Withdrawals or Termination

Subject compensation will not be affected by study withdrawal or termination. Each endpoint will be analyzed using only data for which there is a complete data set relevant to that analysis.

5.5 Premature Termination or Suspension of Study

Study will be terminated if the PI or IRB feels that the rate of adverse events warrants termination or suspension. Study will be suspended if recruiting targets are not met, specifically, if fewer than 70 subjects are recruited at the end of three months, the study will be suspended.

6 STUDY AGENT

6.1 Study Agent(s) and Control Description

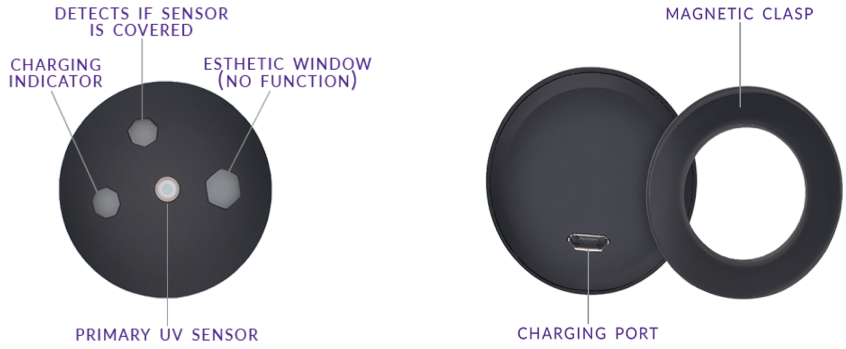
6.1.1 Acquisition

Shade sensors will be delivered to the study coordinator by the sponsor.

6.1.2 Appearance, Packaging, and Labeling

Device:

Figure 6.1.2.1 Shade device



Specifications :

Size: 1.58” diameter, 0.49” height
Weight: 0.48 oz
Battery Life: 4 days (from a full charge); low battery notifications[JC3]
Magnet: Neodynium
Notifications: Light and vibrations
Connectivity: Bluetooth Low Energy
Compatibility: iPhone 5 and above | Android 4.4 and above
Charging: Micro-USB cable included
Recharge time: 1.5 hours

Materials: plastic case
UV Measurement Sensitivity:
Wavelength range: 280-400 nm erythemally weighted
Limit of detection: 0.01 UVI. The UV Index is the unit of intensity recommended by the World Health Organization's INTERSUN working group.
Maximum UV: 16 UVI
Dosimetry: accuracy and precision 1.5 J/cm^2

Software
The software consists of firmware in the device, a mobile application, and backend servers to support it. The mobile application has been designed based on user feedback to highlight issues important to people concerned about their exposure to UV light. Specifically it reports the devices estimate of the current UV Index as well as the user's cumulative exposure for the day in units of J/m2. The software keeps a history of the exposure and allows the user to set a daily limit of UV exposure at which they will receive alerts. The backend manages each user account and stores their historical data to allow retrieval and analysis.
When the device is charged, it indicates connection by momentarily glowing green, then it indicates charging by glowing red. When the device is fully charged, and connected to power, it indicates green. Once powered up, it sends a Bluetooth (BT) signal advertises its presence. In this state it can be paired to a phone using app set to the pairing function. If the device is covered, for example by a jacket, it provides a vibration alert and a mobile phone alert periodically until it is uncovered.

APPLICATION USER INTERFACE

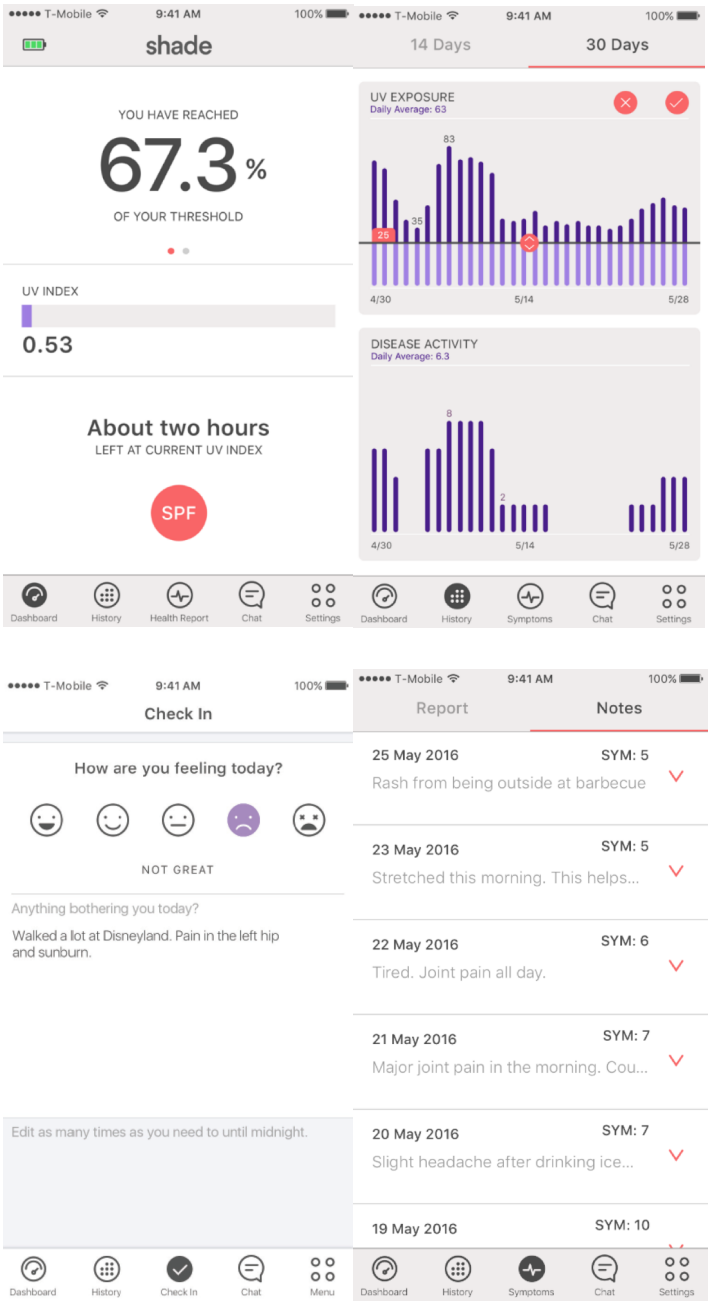
When the device is first activated and paired with a new mobile device an onboarding protocol is run through (see Attachment 4). The application contains five tabs: dashboard, history, symptoms, chat, and settings.
Dashboard:
The dashboard allows the user to visualize their current exposure, total exposure for the day, as well as an estimate of the time remaining during the day that the user can be exposed to the sun at current intensity levels. From the dashboard the user is also capable of logging their sunscreen (SPF) usage during the day. For a period of time after logging the sunscreen (90 minutes) the reported UV dose is reduced by an amount corresponding to the reported SPF.
The history tabs allows the user to visualize their daily UV exposure over the last 12 days.
Symptoms:
From the symptom tab the user is capable of inputting their symptoms with a timestamp that could provide useful feedback to the user on the correlation between symptoms and UV exposure.
Chat:

Chat enables users to receive real-time feedback from the company regarding the Shade device and the mobile application usage. This is also a platform for providing feedback to the company, application troubleshooting, or any other questions, comments, or queries the users may have.

Settings:

The user can manage general application settings from this tab. For example: it is from this tab that a user can pair their Shade sensor to their mobile phone.

Figure 2-3: Shade Application Key Screenshots



ALARMS

In use, the device uses two methods to notify the user. (1) shade device vibration and (2) mobile phone alerts. Notifications are triggered by the following events:

1) UV exposure reaches a 20 percent interval of the user's specified daily limit.

2) The sensor has been covered making it insensitive to UV.

Additionally, the user can trigger both alert methods by covering the proximity sensor with their finger or the vibration alert by triple tapping the battery indicator on the app's dashboard screen (Figure 2-3, first screen).

Packaging:

The device and user guide are supplied in a white 4.7 x 6.25 x 1.5 inch cardboard box labeled 'Shade.'

Labeling:

User instructions are attached as Appendix 1. The device packaging will be labeled with a sticker indicating 'For Investigational Use Only.'

6.1.3 Product Storage and Stability

Store indoors (0-40°C). Product is stable indefinitely.

6.1.4 Preparation

Prior to use, subject must install a device specific application on their mobile phone. The Study Coordinator or a sponsor representative will assist them in this process. As part of the use of this application the user enters an email address. Subjects will *not* enter their own email address and will instead enter a non-functional study email address assigned by the study coordinator. See data management sections for details.

6.1.5 Dosing and Administration

N/A

6.1.6 Route of Administration

N/A

6.1.7 Starting Dose and Dose Escalation Schedule

N/A

6.1.8 Dose Adjustments/Modifications/Delays

N/A

6.1.9 Duration of Therapy

9-12 months

6.1.10 Tracking of Dose

N/A

6.1.11 Device Specific Considerations

The device is worn externally, magnetically affixed to the subject's clothing. The device vibrates to communicate to

subjects when they have accumulated UV dosage and when the device is covered. The mobile application provides similar alerts with accompanying explanatory text.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

Product will be delivered to the study coordinator by the sponsor. The delivery slip will include a receipt with a list of device serial numbers. The study coordinator will acknowledge receipt and return the signed packaging invoice to sponsor. Supplies should be kept in a secure area.

The study coordinator will maintain a device disposition table with the columns: S/N, Subject ID, Date dispensed, Dispensed by (name of study personnel), Date returned, Returned to (name of study personnel), Comments (e.g. working/broken/lost). The device disposition table is considered confidential and should be viewed only by the study coordinator and study monitors, physicians must remain blinded to the device disposition table.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

Cyclobutane pyrimidine dimers (CPD) levels will be measured by ELISA from exposed (cheek) and unexposed (buccal mucosa) skin scrapings. The area from which the cutaneous scraping is collected will be cleaned with an alcohol swab. Using a 15 blade, the epithelial cell will be lightly scraped on the cutaneous cheek and the buccal mucosa. The skin cells will be placed in an eppendorf tube and put on ice. These eppendorf tubes will be transported to a research lab where ELISA testing will be performed by a technician. For each patient, the CPD level from exposed skin will be normalized to the sun protected CPD level measured from unexposed skin. A physician will compare the normalized CPD level of control versus study participants at each timepoint and their average CPD change over time.

Clinical counting of AKs: The physician will identify actinic keratosis based on a visual and textural examination. If the actinic keratosis is large and continuous it will be counted as one actinic keratosis. The actinic keratosis will then be circled and photographed. The photograph will be available in the patient medical record but will not be copied to the CRF. The areas that are identified during the visit will be treated. Photos will be taken at each visit. At subsequent visits, the previous visits, photos will be reevaluated to prevent double counting. All lesions suspected of malignancy will be biopsied and subject to histological examination. These lesions will be reclassified according to histology diagnosis if necessary.

7.1.2 STANDARD OF CARE STUDY PROCEDURES

Skin Check

A standard skin examination will be performed by a dermatologist. The scalp, face, mucous membranes, chest, back abdomen, arms, legs, genitalia, digits will be examined at the first and last visit (V1 and V3). A focused examination of the scalp, face, hands and any other pertinent areas will be performed at the second visit (V2).

Treatment of actinic keratosis

When an actinic keratosis (AK) is identified, the area will be identified with a marking pen. The areas will be photographed and the photos attached to the patient's chart. The areas will then be treated with a destructive modality. The most common technique that will be employed is cryotherapy with liquid nitrogen or curettage of the actinic keratosis. Any AK that is suspicious or resistant to treatment will be biopsied via shave technique. Shave technique is described as the removal of entire lesion using a dermablade with 1-2 mm margins.

Ultraviolet Exposure Counseling

The dermatologist will make the following recommendations to each patient having a skin cancer screening.

-Always use a sunscreen product with a minimum SPF of 30 when going outdoors, even on a cloudy day.
-Avoid exposure to the sun during the peak hours between 10 AM and 4 PM and to stay in the shade when possible.
-Wear protective eyewear during peak sun hours.
-If sunscreen is not available, always wear protective clothing, such as long-sleeved shirts and pants, wide-brimmed hats, and sunglasses with UV protection.
-Routinely examine skin at least once a month for any visible changes or changing lesions.
-Avoid the use of tanning products or tanning beds.
-See your dermatologist yearly for a professional skin exam

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

7.2.1.1 CPD Assay

The CPD Assay will employ a commercial ELISA based test. It will be carried out following a detailed written protocol developed by the investigating laboratory based on the manufacturer's published procedure. The validation of this procedure will be presented by the laboratory manager and this validation along with the protocol will be reviewed by the PI and the sponsor. Once implemented, the procedure will be carried out on clinical samples with attention to good laboratory practice.

7.2.2 Other Assays or Procedures

N/A

7.2.3 Specimen Preparation, Handling, and Storage

Skin scraping will be collected as described in 7.1.1 Study specific procedures.
The tubes containing the samples and any secondary containers will be labeled by: ###-S and visit number
- study subject number ###
- site S which is one of B (buccal mucosa) or S (skin)
- visit number # = 1,2,3

The specimens will be stored in liquid nitrogen or at -80°C in the clinic in a labeled separate container for materials for this study. Samples will remain in this container until collected by laboratory staff.

7.2.4 Specimen Shipment

Skin scrapings will be transferred to the New York Presbyterian Laboratory at 525 East 68th Street, New York, NY 10065. Staff will carry the samples to the clinical lab in an insulated container immersed in liquid nitrogen and then samples will be stored in liquid nitrogen or at -80°C prior to being processed by the laboratory technical staff.

7.3 Study Schedule

7.3.1 Screening

A pre-screening/recruiting phone call will occur before scheduling the screening visit. This call will establish the subjects probable eligibility for the study.
At the screening visit the study coordinator will assess eligibility by checking for inclusion and exclusion criteria and entering these results in the CRF.
Following inclusion/exclusion questions, the study coordinator will obtain informed consent from the subject.
Only subjects who satisfy all screening criteria and provide consent will be enrolled in the study.

7.3.2 Enrollment/Baseline

During the enrollment visit the physician will complete a medical history including an assessment of Fitzpatrick skin type. The enrollment visit will include standard of care counseling on the importance of UV avoidance. For transplant recipients, condition appropriate information will be included.

Ultraviolet Exposure Counseling: as described in 7.1.2 Standard of Care Study Procedures

The enrollment visit will include the skin check described in 7.1.2 Standard of Care Study Procedures.

Skin Check: as described in 7.1.2 Standard of Care Study Procedures

Treatment of Actinic Keratoses as described in 7.1.2 Standard of Care Study Procedures.

At the conclusion of the enrollment visit the study coordinator will discuss with enrolling physician for for determination of Fitzpatrick skin type. The coordinator will then assign the subject to treatment or control groups following the procedure in section 10.6.1. The subject's assignment will be noted on the randomization table to be kept confidential to the coordinator and study monitors.

The coordinator will meet with the subject in a separate room to schedule the first follow up visit. If the subject is in the treatment arm, in this meeting the subject will be given the box with the Shade sensor. The coordinator or a sponsor representative will observe and support the subject in the process of opening the box and installing the application on their phone. At this time the coordinator will assign a study email address to the subject and enter that address in the randomization table and an electronic table along with the subject's actual email address.

7.3.3 Follow-up

A focused examination of the scalp, face, hands and any other pertinent areas will be performed at the follow up visit(s). AKs will be identified and photographed. Any other suspicious lesions will be biopsied as described as above. AKs will be treated as previously described.

The study coordinator will maintain the schedule of follow up visits and will contact subjects via phone or email. In the event that a subject in the treatment arm is having difficulty achieving compliance, the study coordinator will be available for counseling, training, to provide replacement of broken or lost devices, and encouragement. Calls will be logged in the study binder.

7.3.4 Final Study Visit

For the final visit, a standard skin examination will be performed by a dermatologist. The scalp, face, mucous membranes, chest, back abdomen, arms, legs, genitalia, digits will be examined. Any AKs will be identified, photographed and treated as previously described. Any suspicious lesions will be biopsied. If the patient is in the study arm, the device will be collected by the study coordinator at this visit.

7.3.5 Early Termination Visit

Subjects who withdraw consent or otherwise voluntarily leave the study will be offered the opportunity to participate in the next visit scheduled for the study.

Subjects who are dropped from the study for any reason will be contacted by phone to explain the reason they have been dropped from the study. An early termination visit is not required.

Subjects who terminate early will be asked to return their Shade device and will be given the same offer to obtain a new device of their own as subjects who complete the study.

The study coordinator will fill out a study termination form for all subjects including those who leave early.

7.3.7 Schedule of Events Table

Procedures	Prior to enrollment	Enrollment	Visit 1	Before visit 2	Visit 2	Before visit 3	Visit 3	AE Visit
Screening call	X							
Screening questions		x						
Informed consent		x						
Medical history		x						
Patient survey			x		x		x	
Dermatology Visit			x		x		x	
UV counseling			x		x		x	
Full Skin Check			x		x		x	
Focused Skin Check			x		x		x	
Collect skin scraping (WCM only)			x		x		x	
Randomization			x					
Compliance engagement				x		x		
Return study materials							x	
Condition driven medical exam								x

Screening call:
Screening questions: These are listed in the CRF
Informed consent: As approved by IRB
Medical history: Key questions listed in CRF
Patient survey:
Dermatology visit:
Collect skin scraping:
Randomization:
Compliance engagement:
Return study materials: See section 7.9

7.4 Justification for Sensitive Procedures

There are no sensitive procedures in this study.

7.5 Concomitant Medications, Treatments, and Procedures

Concomitant medications, treatments and procedures will be recorded in the CRF.

7.5.1 Precautionary Medications, Treatments, and Procedures

None

7.6 Prohibited Medications, Treatments, and Procedures

The use of topical and oral medications prescribed as field treatment for actinic damage (i.e., imiquimod, acitretin, etc.) would be prohibited during this study. Targeted topical treatment of biopsy-proven non melanoma skin cancer (e.g. imiquimod) would be allowed at the provider's discretion. Any treatment of actinic keratoses or any biopsies of suspected malignancies by an outside dermatologist would be prohibited during the study

7.7 Prophylactic Medications, Treatments, and Procedures

None

7.8 Rescue Medications, Treatments, and Procedures

None

7.9 Participant Access to Study Agent At Study Closure

At the conclusion of the study subjects in the treatment arm will

1. Return the Shade device used in the study.
2. Receive a printout of their UV history from the study coordinator.
3. Delete the shade mobile application from their phone.

All subjects will

4. Choose between receiving the final study compensation at the visit or a coupon usable to purchase a new sensor. The coordinator will explain that if they use the coupon, Shade will know that they participated in the study. But Shade will not know their subject ID and will therefore not be able to connect their identity to medical records provided in the study.

8 ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

The primary safety endpoint is the number of adverse events related or possibly related to the device or sun exposure experienced within the study period. To test this hypothesis the number of adverse events related or possibly related to the device or sun exposure experienced by the treatment group should not be significantly greater than the number of adverse events related or possibly related to the device or sun exposure experienced by the control group throughout the duration of the study. Adverse events will be categorized by type, duration, severity, relationship to the study device and need for treatment.

8.1.1 Definition of Adverse Events (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

8.1.2 Definition of Serious Adverse Events (SAE)

- Any untoward medical occurrence that at any dose:
- Results in death,

- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated problems include any incident, experience, or outcome that meets all of the following criteria:

1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2) related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

Classifications often include the following:

· **Mild**: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.

· **Moderate**: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning

· **Severe**: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

Severity is not synonymous with seriousness. A severe rash is not likely to be an SAE. Likewise, a severe headache is not necessarily an SAE. However, mild chest pain may result in a day's hospitalization and thus is an SAE.

8.2.2 Relationship to Study Agent

Adverse events may be caused by one or more of the following:

1. the procedures involved in the research;
2. an underlying disease, disorder, or condition of the subject; or
3. other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

In general, adverse events that are determined to be at least partially caused by (1) would be considered related to participation in the research, whereas adverse events determined to be solely caused by (2) or (3) would be considered unrelated to participation in the research.

8.2.3 Expectedness

AEs must be assessed as to whether they were expected to occur or unexpected, meaning not anticipated based on current knowledge found in the protocol, investigator brochure, product insert, or label. Categories are:

· ***Unexpected*** **-** nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or investigator brochure.

· ***Expected*** **-** event is known to be associated with the intervention or condition under study.

Relatedness

The potential event relationship to the study intervention and/or participation is assessed by the site investigator. A comprehensive scale in common use to categorize an event is:

· *Definitely Related*: The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.

· *Possibly Related:* An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.

· *Not Related:* The adverse event is clearly not related to the investigational agent/procedure. - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

Mild sunburns, not requiring medical treatment, are expected to be over reported in the treatment group because of their constant communication with the application. These will not be considered AE's for the purposes of the safety endpoint.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

Adverse events reported will be assessed and followed up as soon as practical. Subjects reporting adverse events will be contacted by the study coordinator to schedule an assessment. Follow up timing will be sufficient to meet the following reporting requirements.

Unexpected fatal or life-threatening suspected adverse reaction reports:

The sponsor (or sponsor-investigator) must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but no later than 7 calendar days after the initial receipt of the information.

Other reporting requirements:

The sponsor (or sponsor-investigator) must also notify the FDA and all participating Principal Investigators (in multi-site studies) in an safety report about potential serious risks, from clinical trials and any other source, no later than 15 days in the following cases:

· *Serious and unexpected suspected adverse reactions.* Any suspected adverse reaction that is both serious and unexpected must be reported. The report must proceed only if there is evidence to suggest a causal relationship between the drug and the adverse event.

· *Finding from other studies.* Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under serious and unexpected adverse reactions above) must be reported whether or not conducted under an IND or whether or not conducted by the investigator, that suggest a significant risk in humans exposed to the drug.

· *Increased rate of occurrence of serious suspected adverse reactions.* Any clinically important increase in the rate of serious suspected adverse reactions over that listed in the protocol must also be reported.

8.4 Reporting Procedures

8.4.1 Adverse Event Reporting

If any medical event reaches the threshold of an adverse event (AE) as judged by a treating physician, the AE will be reported by study staff or medical staff within 24 hours using both email and telephone to the clinical PI, the study PI and the IRB.
Appropriate action will be taken by the clinical PI and reported in writing to Shade and the IRB within 72 hours.
A written summary of any Adverse Events and their disposition will be submitted by the study PI (E. Dumont) to the funding NIH I/C within two weeks of receiving the written disposition from the clinical PI.

8.4.2 Serious Adverse Event Reporting

As in 8.4.1

8.4.3 Unanticipated Problem Reporting

Unanticipated problems with the device or application will be reported to the study coordinator who will relay the reports to Sponsor. These will be managed by the sponsor using their process for Corrective and Preventive Actions. If a device is lost or becomes inoperable, a new device will be shipped to the subject by the study coordinator. Sponsor and study coordinator will communicate regularly about the inventory of devices and resupply as needed.

8.4.4 Events of Special Interest

The study team has not defined any events of special interest.

8.4.5 Reporting of Pregnancy

Pregnancy will be noted on the CRF as a change in health status. Pregnancy will not result in exclusion from the study.

8.5 Study Halting Rules

The study can be halted at the request of the sponsor, the funding organization, the principal investigator or the IRB. It is expected that the study would be halted in the event that one or more of these reach the conclusion that as result of reported AE's it is unethical to continue the study.

8.6 Safety Oversight

Study staff will record all visits (regularly scheduled and others) and any hospitalization events.

Safety Monitoring

a. Adverse events: If any medical event reaches the threshold of an adverse event (AE) it will be reported and handled as described in 8.4.1.
b. Overall rates of hospitalization and occurrence of AK will be reported by Shade to the clinical PI and the IRB every six months until the study closes.
c. Final rates of hospitalization and occurrences of AK will be included in the final study report.
d. The Shade device does not require an FDA issued IDE. Shade, in consultation with its legal consultants, has determined that is a non-significant risk device because it is not an implant, is not used to sustain human life and is not used in the diagnosis or treatment of disease, and does not otherwise present a significant health risk. As such the device is subject to abbreviated requirements under 21 CFR 812.2(b)

- It will only be used in at risk-populations with IRB approval including monitoring and consent.
- The devices will be labeled 'Investigational Use Only'
- All FDA requirements concerning data reporting, monitoring and promotion will be observed. Shade will request an IRB determination that the device is not significant risk prior to the submission of the study protocol.

Shade may also request an FDA determination of non- significant risk prior to initiation of this study.

9 CLINICAL MONITORING

All clinical data will be recorded on CRFs and monitored by a representative of Shade who may be an employee or an external study consultant. Monitors will perform source-data verification prior to study analysis. The data monitor will ensure that subject confidentiality is not breached by reviewing each CRF for the presence of identifying information. Monitoring visits will be held within two weeks of the first day of scheduled subject visits and continue periodically at the discretion of the sponsor but in no case less than at at six month intervals until study closeout. To facilitate an orderly and timely analysis and to avoid an accumulation of data queries at closeout, there will be a monitoring visit four to six weeks before the end of data collection. At the conclusion of each monitoring visit a report indicating any issues with data, outstanding queries or protocol compliance issues. This report will be shared with Shade and the clinical PI. The results of monitoring visits and queries will be made available to the funding agency's project officer.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical and Analytical Plans

The statistical analysis of the study is the responsibility of the study statistician. Intermediate data reviews will be conducted after 6 months to check for potential problems with data integrity.

10.2 Statistical Hypotheses

The general hypothesis is that sun damage will be lower in the treatment group. The null hypothesis is that sun damage is the same or higher. Below there is a more precise statement of the hypothesis for each study aim.

10.3 Analysis Datasets

Datasets will be prepared by the study coordinator from case report forms. The tables will be formatted as requested by the study statistician and will be monitored.

10.4 Description of Statistical Methods

Actinic keratosis (AK) is a frequent pre-cancerous skin lesion caused by damage from ultraviolet exposure. Without treatment, 1-2% of these lesions evolve into squamous cell carcinoma (SCC).[19] Therefore, the number of AKs reflects the effect of UV exposure and the risk for SCC. Transplant patients are at high risk of skin cancer because of their immunosuppressive medications required to prevent organ rejection. Morbidity/mortality of SCC in this patient population can be as high as 25%.

The primary outcome of this trial will be a statistically significant reduction by at least 25% in the cumulative number of newly developed AK lesions between the control and the study group.

AK lesions on sun exposed skin areas (scalp, face, hands) will be counted and reported by dermatologists at enrollment and at each subsequent visit. AKs are defined as keratotic macule(s) or papule(s) on an erythematous base by dermatological examination. In addition to the enrollment visit, this study will include a follow up dermatological visit after the summer. For each patient, the number of newly occurred AKs will correspond to the cumulative AK counts during the study period. To insure that only new occurrences of AK lesions after V_1 will be counted, data from subsequent study visits will include the location of AK lesions and pictures of the lesions.

10.4.1 General Approach

All tests will be two-tailed with the significance level set at 0.05. Analysis will be performed using STATA statistical software (StataCorp. 2015) or R (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

#1 (Primary): Quantify the impact of Shade on the cumulative number of new actinic keratoses developed over the study period.

To test our primary aim, we will perform a control versus study group analysis. The study group will receive a Shade sensor and Shade app while the control group will standard of care sun avoidance counseling. The study will be randomized and single-blinded as described in section 10.6.1. This will also allow us to control for the effect of UV level variation on the primary outcome since the two groups will have balanced enrollment dates. All the patients will receive recommendations about UV exposure protection as defined by the recommendations of the American Academy of Dermatology and the National Cancer Institute.

Patients who will have used the Shade sensor for less than 15% of the days over the study period will be excluded from these analyses. We will use a Student's t-test with the following null and alternative hypothesis:
H_0: mean $^{C}_{t12}$ (AK) = mean$^{I}_{12}$ (AK)
H_a: mean$^{C}_{t12}$ (AK) $\neq$ mean$^{I}_{t12}$ (AK)
where mean$^{C}_{t12}$ (AK) is the averaged cumulative number of AK between enrollment follow up of controls and mean$^{C}_{t12}$ (AK) is the averaged cumulative number of AK of intervention patients.

In this analysis, demographic and clinical factors such as gender, age, baseline count of AKs, skin type, immunosuppressive treatment and comorbidity can be confounding factors. To test and control for confounding, demographic and clinical data (skin type, living area, gender, age, count of AK at enrollment, immunosuppressive (IS) treatment, level of immunosuppression and comorbidity) will be collected. We will use a stepwise multivariate approach with backward selection: 1) the effect of potential confounding factors will be tested using the same statistical tests, 2) factors with p-value <0.2 and less than 25% of missing values will be included in the multivariate model and 3) only covariates with significant adjusted p-value (<0.05) will be kept in the final model. Clinically relevant interactions will also be tested (e.g. skin type, gender, age) and kept in the final model if significant. The adjusted effect of Shade use will be estimated using a multivariate linear regression.

10.4.3 Analysis of the Secondary Endpoint(s)

#2 (Secondary): Quantify the impact of Shade on the numbers of new AK's observed at the final visit
This analysis will follow the same procedure as the primary analysis but will only include AK data from the final visit.

#3 (Secondary): Quantify the impact of Shade on the numbers of new cutaneous squamous cell carcinomas confirmed by histology during follow up over the study period.

To test the early effect of Shade on skin cancer risk and the robustness of our findings, we will perform a longitudinal analysis to test a reduction by at least 25% of squamous cell carcinoma. The effect of Shade use will be estimated using a single mixed linear model (with random intercept and slope) for repeated (longitudinal) data including study group and time since enrollment as explanatory variables. A similar stepwise multivariate approach with backward selection as described in the primary aim will be perform to take into account confounding factors.

#4 (Secondary): Quantify the impact of Shade on the number of new nonmelanoma skin cancers (basal cell carcinomas, cutaneous squamous cell carcinomas) confirmed by histology over the study period.

To test the early effect of Shade on skin cancer risk and the robustness of our findings, we will compare the cumulative numbers of new nonmelanoma skin cancers between the control and study group and test a reduction by at least 25% of non-melanoma skin cancer s as secondary outcome, using a t-test. A similar stepwise multivariate approach with backward selection as described in the primary aim will be perform to take into account confounding factors.

#5 (Secondary): Test the correlation between measured UV exposure and the number of new actinic keratoses.

We will test the correlation between the cumulative UV exposure and the number of AK lesions at each time point using a Pearson correlation test or a non-parametric Spearman test if the requirements for the parametric test are not met. A significant correlation will be defined as $\rho > 0.2$ and p-value < 0.05. UV exposure will be defined as the cumulative UV exposure in erythemally-weighted J/m^2 at each time point since enrollment.

#6 (Secondary): Test the correlation between measured UV exposure and the number of new nonmelanoma skin cancers.

We will test the correlation between the cumulative UV exposure and the number of new nonmelanoma skin cancers using a Pearson correlation test or a non-parametric Spearman test if the requirements for the parametric test are not met. A significant correlation will be defined as $\rho > 0.2$ and p-value<0.05. UV exposure will be defined as the cumulative UV exposure in erythemally-weighted J/m^2 at each time point since enrollment.

#7 (Secondary): Quantify the impact of Shade on keratinocyte DNA damage approximated by the measurement of cyclobutane pyrimidine dimers by ELISA.

Cyclobutane Pyrimidine Dimers (CPD) are induced by UV exposure in a dose dependent fashion.[6] UV exposure can lead to immediate CPD increase; therefore measurement of CPD following the delivery of a known UV dose allows for a biological readout of UV effects. In addition, CPD levels represent an equilibrium between UV induced formation and DNA repair; therefore, they can also reflect chronic UV exposure.[21]

CPD level will be measured from ELISA from exposed (cheek) and unexposed (buccal mucosa) skin samples collected. For each patient, the level from exposed skin will be normalized to the basal CPD level measured from unexposed skin. Correlation of CPD level to Shade UV measurement 24 hours prior to collection will allow for an acute UV biological validation that Shade measured UV levels correspond to levels of CPD damage (using Pearson correlation test or a non-parametric Spearman test). We will also compare the normalized CPD level of control versus study participants at each timepoint and their average CPD change over time using a t-test. These comparisons will assess the accuracy of Shade measurements as it relates to chronic UV exposure.

The outcome will be a statistically significant reduction by at least 25% of the normalized CPD level of exposed keratinocytes.

#8 (Secondary): Quantify the impact of Shade on patients' quality of life assessed by PROMIS (Patient-Reported Outcomes Measurement Information System) in the fields of anxiety (Mental Health), depression (Mental Health), and Ability to Participate in Social Roles and Activities (Social health).

To assess the impact of Shade on quality of life, patients will be surveyed using short form paper versions of PROMIS (Patient-Reported Outcomes Measurement Information System) scores in the fields of depression, anxiety, and the ability to participate in social roles and activities. PROMIS survey will be performed at each visit. We will compare the change in PROMIS scores between group and study using a t-test at each time-point.

The outcome will be assessed for statistical significance (p-value of change in PROMIS score between groups) and clinical significance (changes of 3 points on a single score are generally considered meaningful to subjects).

#9 (Secondary): Assess sensor usage in the study patient population and compare characteristics of observant vs non-observant and responsive vs non-responsive patients.

To assess sensor usage, we will estimate the overall percentage (and 95% confidence interval) of days used in the study patient population, the average (and standard deviation) and median (and quartile) of the daily UV threshold set by the patients and the percentage of days below and above the UV threshold.

The Shade sensor and the mobile application enables users to decide, by looking at self-reported symptoms and daily cumulative UV exposure over 15 and 30 days, how much UV exposure in J/m2 they would like to manage per day, which we call the daily UV threshold. Users can select a daily UV threshold that is lower than their previous maximum daily UV exposure. Of course, users are free to go beyond this threshold if they chose to and the app will let them know in real time by how much they have exceeded their threshold. The threshold can be adjusted at any time through the app. The Shade app does not make any recommendation regarding the daily threshold. Note that each subject will be individually counseled to minimize UV exposure.

We will also quantify the percentage of observant and non observant patients, as well as the percentage of responsive and non-responsive patients. While observance will be based on the use of the sensor, responsiveness will be based on "safe" UV behaviors. Observance will be defined as at least 50% of days used, poor observance between 15% to 50% and non-observance as inferior to 15%. Responsiveness will be defined as less than 15% days over the UV threshold and more than 85% of days with an UV threshold set within one standard deviation of the study group's average UV threshold. Conversely, non-responsiveness is defined as more than 15% days over the UV threshold or more than 85% of days with an UV threshold set above one standard deviation of the study group's average UV threshold.

The sociodemographic and clinical characteristics of observant, poorly observant, non-observant, responsive and non-responsive patients will be assessed separately and compared using Student's t-tests for quantitative characteristics and χ^2 for categorical characteristics. These comparisons will provide useful information to better understand the determinants of UV behaviour change.

To be conservative, only non-observant subjects (<15% of days use) will be excluded from the analyses while poorly and non-responsive patients will be included. The comparison of their characteristics will rule out a selection bias.

#10 (Secondary): Assess feasibility of the intervention for kidney transplant recipients through report of their rates for compliance and retention.

Rates will be reported but are not expected to be analyzed for significance.

10.4.4 Safety Analyses

No safety analyses are planned.

10.4.5 Adherence and Retention Analyses

See specific Aim #8.

10.4.6 Baseline Descriptive Statistics

Demographic statistics (# and % male/female, %ethnicity, % race) will be collected and reported.

10.4.7 Planned Interim Analyses

10.4.7.1 SAFETY REVIEW

As this is a low-risk study, no specific safety review will be conducted. See the handling of Adverse Events for mechanisms for safety assurance.

10.4.7.2 EFFICACY REVIEW

N/A

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

N/A

10.4.9 Multiple Comparison/Multiplicity

The planned analyses do not include multiple comparisons.

10.4.10 Tabulation of Individual Response Data

Clinical data tables will be reduced into a table of individual responses for analysis as follows:

Column	**Source (name of CRF with data)**
SubjectID	N/A
AK baseline (count)	Actinic Keratosis
AK follow up (cumulative count)	Actinic Keratosis
NMSC baseline (count)	NMSC
NMSC follow up (cumulative count)	NMSC
Observant % of days	Compliance database
Responsive Y/N	Shade database: days with UV limit below 90% of exposures
CPD R 0	Lab data
CPD R 12 month	Lab data
MHA 1	PROMIS MHA visit 1
MHA 2	PROMIS MHA visit 2
MHA 3	PROMIS MHA visit 3
MHD 1	PROMIS MHD
MHD 2	PROMIS MHD
MHD 3	PROMIS MHD
SHP 1	PROMIS SHP
SHP 2	PROMIS SHP
SHP 3	PROMIS SHP
UV Ave	Sensor data
AE (count)	CRF
comment	

group	Randomization
exclude	

10.4.11 EXPLORATORY ANALYSES

None

10.5 SAMPLE SIZE

The most efficient approach to performing the power calculation for this study via Monte Carlo simulation as the underlying phenomenon, AK rate, is best modeled by a Poisson distribution.[22]

As a starting point, we took the distribution of AK rates from actual clinical data. The data were assembled by querying EPIC on 2014 visits of kidney transplant patients to dermatology (this subset of the population will have fewer AK's than the non-transplant subjects and therefore use of this distribution will err on the side of caution toward overpowering the study). For each visit in which the dermatologist chose to treat by LN2 destruction, the query retrieved the number of procedures performed. This approach is conservative as the input data potentially underestimates AK count as some AK's may not have been treated.

The structure of the Monte Carlo was straightforward. A set of potential study sizes (N recruited) and effect sizes were chosen. For each input condition, two thousand random experiments were performed. In each of these interactions, baseline AK rates were drawn from the clinically observed distribution of AK's. Subjects were sequentially assigned to treatment or control groups. Observed AK rates were generated using a Poisson distribution for each visit. The analysis expected for the study was then performed. In this analysis the total count of AK's for each subject was obtained and the means and distributions compared for directionality (AK_treated < AK_control) and significance (p-value from a one-tailed t-test).

Analysis was performed in R (R Open 3.2.3) with statistical calculations and random number generation using the base and stat libraries.

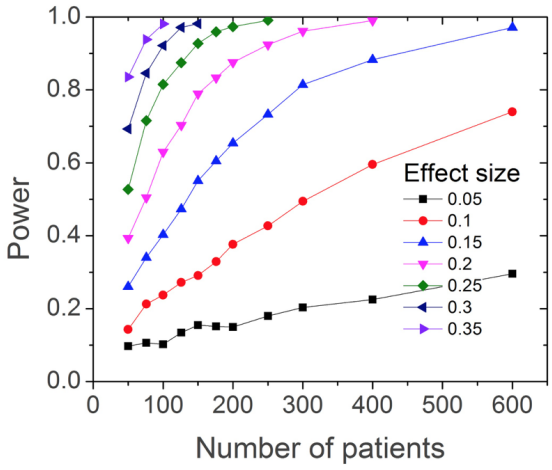


Figure 10.5.1. With an effect size of 0.25 and recruitment of 100 patients (50 treatment, 50 control) we predict a power of 0.81.

10.6 Measures to Minimize Bias

This study will be partially blinded. We will divide study participants into 2 groups. The experimental group will wear an ultraviolet sensor which will record their UV exposure. The control group will receive standard of care counseling about photoprotection from their dermatologist. The study coordinator will spend the first 10 minutes of the visit with each patient reviewing any issues related to the study, including sensor related issues. The study coordinator will remind the patient at each visit to put the sensor away from view and to not discuss any sensor related questions to the dermatologist. The dermatologist will then come in and perform a total body skin examination. Actinic keratosis will be identified, circled and photographed. The actinic keratosis will then be treated via a destruction method. Any potential skin cancers will be biopsied and sent for pathology. Cyclopyridimine butane dimer (CPD) analysis will be obtained via light curettage of the skin and mucosa. They will be sent to a lab and the data will be processed. A different physician will evaluate the results and will not have access to clinical data. This physician will remain completely blinded to the study.

10.6.1 Enrollment/ Randomization/ Masking Procedures

The randomization schedules will be developed prior to the enrollment of the first subject. There will be one schedule for Fitzpatrick types I-II and a second schedule for Fitzpatrick types III and higher. The randomization schedule is a simple list of assignments to the groups 'Treatment,' meaning that the subject will be given the Shade device and mobile application and 'Control,' meaning that the subjects will be given only the standard of care counseling to avoid UV.
The following sequence of events at enrollment will ensure that the treating physician will be blinded to the subject assignment:

(1) visit with study coordinator for screening, informed consent, and medical history.

If the subject passes screening and grants consent

(2) physician visit.

During the physician visit, the study coordinator will take the next randomization from the randomization schedule. This schedule will be prepared by the sponsor in such a manner that the coordinator remains blind to the next assignment until it is requested. The sponsor has latitude to implement this using any reasonable physical or computational system. The subject assignment will be entered on the randomization schedule available only to the study coordinator and the study monitor.

(3) wrap up conversation with study coordinator.

After the physician visit the study coordinator will sit with the subject in a separate room. The next visit or visits will be tentatively scheduled. If the subject is in the treatment group, the device will be provided and either the coordinator or a sponsor representative will work with the subject to setup the mobile application and ensure that subject understands how to use the device.

At subsequent visits subjects in the treatment group will be instructed to

(1) avoid discussing their assignment with the physician.
(2) place the shade sensor in a purse or pocket out of view of the physician
(3) mention to the study coordinator if the subject of the assignment came up in conversation with the physician.

10.6.2 Evaluation of Success of Blinding

The study coordinator will note any failures of blinding in the randomization table.

10.6.3 Breaking the Study Blind/Participant Code

The study blind will be broken after PI and sponsor agree that the clinical data tables are complete and that all remaining data queries have been followed to their logical conclusion.

Just prior to breaking the study blind, the study data tables will be frozen.
The blind will be broken by the study coordinator who will provide the full team with a copy of the randomization table.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Sources of data for the CRF include:
Medical records created by the examining physician
Survey data filled in by the subjects
Other medical records stored in the study site electronic medical records system

The study coordinator will have access to all of these data sources.
The examining physician and the PI will have access to all of these data sources.
The study monitor will have supervised access to these sources during monitoring visits. It is the responsibility of the study coordinator to assist study monitors in source data verification. Study monitors will record only non-identifying information in their queries.

Data queries will include the subject ID and the nature of the query.

12 QUALITY ASSURANCE AND QUALITY CONTROL

The study team will implement quality assurance and quality control measures documented in this protocol. The intent of the protocol and the commitment of all staff is to be in compliance with good clinical practice, including its requirements for quality management.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Ethical Standard

This study is conducted under the ethical standards described in ICH E6. Please see the compliance statement on the PI sign-off page at the beginning of the protocol for details.

13.2 Institutional Review Board

This study will be under the review of the Weill Cornell Institutional review board.

13.3 Informed Consent Process

Informed consent will be obtained at the beginning of the screening phase of the first visit. No subjects will be enrolled in the study unless they have completed the screening and provided consent.

13.3.1 Consent/assent and Other Informational Documents Provided to Participants

See Appendix 2 Informed Consent, and Appendix 3 Advertising Material

13.3.2 Consent Procedures and Documentation

At the initiation of the screening and consent process, a subject ID will be assigned, and the subject ID entered into the central table of subjects. Once consent is provided, the IC form will be added to the study binder. At this point the subject table value, 'Screen passed' will be entered in the table.

13.4 Participant and data Confidentiality

At the study site, medical and research staff will have access to patient information for the purpose of transferring this information to non-identifiable CRFs. Study data monitors will match clinical data to CRFs under supervision of the study coordinator. Sponsor will maintain, any identifiable private information will be encrypted and stored in Shade's HIPAA compliant storage. No identifying information will be available to sponsor except during monitoring activities.

13.4.1 Research Use of Stored Human Samples,Specimens or Data

The study team may use any stored samples, specimens or data for future research or analysis. All future analyses will respect subject confidentiality. Non-identifying study data will be retained by the sponsor and made available to any qualified researcher upon request as described in section 14.4.

13.5 Future Use of Stored Specimens

Stored specimens may be subject to future analysis for research purposes related to or unrelated to the purpose of this study. Such analyses will respect subject confidentiality.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Collection and Management Responsibilities

Clinical data collection is the responsibility of the Weill Cornell team with the PI having overall responsibility for supervision and the study coordinator having responsibility for execution of data collection. Study coordinator will prepare monthly reports summarizing progress on data completion.

The sponsor will review and monitor data periodically.

14.2 Study Records Retention

IRB records will be retained by WMC for no less than three years, and research records will be retained by WMC for no less than three years after the completion of the research.

14.3 Protocol Deviations

Protocol deviations will be reported to the sponsor and the IRB within 72 hours. The following events are expected and should be marked on the CRF but do not require reporting as deviations:

1. Rescheduled visit. While visits should be scheduled within 7 days of the target visit date, visits may be rescheduled within 21 days of the visit target date.
2. Screen fail. A subject may be enrolled based on passing screening questions but subsequently dropped if there is evidence in their medical record that they have failed screening. In that event the subject's CRF will indicate a screen fail (by initialing the appropriate CRF) and the subject will be dropped from the study.

14.4 Publication and Data Sharing Policy

Sponsor and Investigators are committed to enhancing the value of research and furthering the advancement of public knowledge as well as to the development of its commercial products and the protection of its intellectual property. We recognize that this project will result in the collection of data useful to the research community. Therefore, final research data will be shared openly and timely in accordance with the most recent NIH guidelines (http://grants.nih.gov/grants/policy/data_sharing) while being mindful that the confidentiality and privacy of participants in research must be protected at all times. Timelines for distribution of data will vary depending on any required restrictions in accordance with federal and/or institutional policies and guidelines. In general, we expect the

data will be available through publications, presentations at scientific symposia and seminars. In some cases, Shade may determine that a licensing program may be necessary to better serve the public and the research community whether or not patents have been filed. Efforts will be made to publish our research findings in scientific journals. All final peer-reviewed manuscripts that arise from this proposal will be submitted to the digital archive PubMed Central.

In order to protect the identity of subjects in this study, a more detailed discussion of the clinical data collected in this project is required. Data will come from two sources which will be handled differently.
Data collected from the clinic itself will include subject demographics including race, gender, Fitzpatrick skin type, in addition to key metadata related to the study hypothesis including transplant status, prior cancer history and prior history of actinic keratosis. These data will be published in an appropriately aggregated tabular form.

The second source of data will be from the Shade device and software. While more specific, and potentially identifying, data may be collected by the device, as discussed in the human subjects protection section, potentially identifying data will not be available to study staff. Device data will include usage data, sun exposure, self-reported adherence to sun protection guidelines, self- reported symptoms of sun exposure including erythema. Subject level device data is likely to include subgroups of fewer than 20 people with specific combinations of metadata. For that reason, there will no release of subject level device data with direct links to metadata. Subject level data will be linked to Fitzpatrick skin type, gender and age rounded to the nearest multiple of 10 as well as the assignment of the subject to the test or control group. These data will be plotted, statistically analyzed and tabulated for publication. To encourage use of the data, subject level device data will be made available on request to qualified researchers including to NIH staff who agree to restrictions against public release of the data, attempts to identify study participants, destruction of the data after analyses are completed, reporting responsibilities, restrictions on the redistribution of the data to third parties, and proper acknowledgement of the data resource. Requests will be made directly to Shade by email through contact information to be provided on its web site and included in each publication based on these data. These data will be shared without fee through a single use web link which will enable the secure download of subject level device data in .csv format.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

N/A

16 CONFLICT OF INTEREST POLICY

The WC conflict of interest policy applies to all personnel involved in this study. The policy is available at https://www.dfa.cornell.edu/policy/azindex/conflicts
It is expected that all personnel will complete training in this policy which is available through the CITI program with links available at http://researchintegrity.weill.cornell.edu/conflicts_management_office/

17 REVISION HISTORY

17.1 VERSIONS

2017A1_v1	Approved date:
2017A_v2_1	Submitted date:

Change summary: remove requirement for subjects to be kidney transplant recipients.
motivation: on examination, the recruiting pool of KTR is small and there is not an underlying medical belief that the risk

or mechanism is different for the non KTR pool, with significant and recurring AK's.

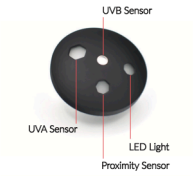
17.2 Managing Protocol Changes for continuing subjects

All subjects who signed consent forms prior to the protocol change will be reconsented at their next visit.
Visits one and two are unchanged. Visits 3 and 4 have been removed from the protocol. At the time of this protocol change some subjects have completed visit 2. These subjects, who were scheduled to have a visit that is no longer part of the study design will be informed that this visit is no longer required. As no action is required of these subjects there will be no need to reconsent until their final study visit. For subjects who have not yet had their 3 month visit, reconsent at visit 2 will be appropriate.

APPENDIX 1 USER INSTRUCTIONS

WHAT'S IN THE BOX

SHADE SENSOR



MAGNETIC CLASP

CHARGING CABLE

SIMPLE SETUP

01
Start by charging the sensor. The light on the sensor will turn from orange to green when it is fully charged.

02
Download the app by visiting wearshade.com/iOS from your iPhone.

03
Launch the app to create an account and follow instructions to pair the sensor to your iPhone.

FOR MORE, VISIT
HELP.WEARSHADE.COM

HOW TO #WEARSHADE

04
Separate the magnetic clasp from the sensor by sliding it off with your thumb.

05
Position the sensor on your upper torso and reattach the clasp. Try to wear it in the same position every day.