EBIRE: Phase I Study of High Fluence LED-Red Light in Fitzpatrick Skin Types I to III

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Abstract

Objective: To determine the safety of high fluence light emitting diode-red light (HF-LED-RL) phototherapy in Fitzpatrick skin types I to III.

Research Design: This study will be a single-blind, dose-escalation, randomized controlled, Phase 1 study of HF-LED-RL in Fitzpatrick skin types I to III. Subjects with Caucasian or white skin color (Fitzpatrick skin types I, II, or III) will be enrolled sequentially in groups of five (three subjects randomized to HF-LED-RL phototherapy and two subjects randomized to mock therapy). This study is based on the results of the previous “Phase 1 study of LED-RL in Human Skin” (VA file number: 15-12-00756), which demonstrated that HF-LED-RL doses up to 320 J/cm2 was safe in all skin types. One male subject with Fitzpatrick skin type V had an adverse event of a blister with HF-LED-RL at fluence of 480 J/cm2. The other two subjects, who were of Fitzpatrick skin types I to III, treated with HF-LED-RL at fluence of 480 J/cm2 had no adverse event. Therefore, we wanted to explore the safety of HF-LED-RL at doses of 480 J/cm2 and 640 J/cm2 in Fitzpatrick skin types I to III.

The initial group will receive doses of 480 J/cm2 of HF-LED-RL or mock therapy at the Sacramento VA Medical Center Dermatology Clinic three times a week for three consecutive weeks, which is a standard phototherapy regimen based on phototherapy guidelines. An additional group (Group 2: 640 J/cm2) will be sequentially enrolled to receive a higher dose of HF-LED-RL phototherapy or mock therapy. If there is a single adverse event in either Group 1 or Group 2, we will repeat that same dose in a new cohort of five additional subjects (Group 1A or 2A, respectively). This is to account for a

possible outlier effect. The maximally tolerated dose (MTD) will be defined as the dose level below the dose producing unacceptable but reversible adverse toxicity in two or more subjects. After either a MTD has been established or the endpoint dose of 640 J/cm2 has been achieved, an additional 27 HF-LED-RL phototherapy subjects (for a total of 30 or 33) and 18 mock therapy subjects (for a total of 20 or 22), determined randomly, will be enrolled for a total of 50 subjects, such that it can be concluded with 95% confidence that fewer than 1 person in 10 will experience an adverse event.

Methods: Healthy subjects, any sex, ethnicity, and age with Fitzpatrick skin types I to III that do not meet exclusion criteria and whose nondominant proximal anterior forearm is wide enough to ensure reproducible placement of HF-LED-RL phototherapy or mock therapy hand-held unit will be recruited. Subjects with light-sensitive conditions or on photosensitizing medications, subjects with open wounds, diabetes, fibrotic skin diseases or other skin conditions affecting the nondominant proximal anterior forearm will be excluded from the study. Subjects with tattoos that cover the procedure site will also be excluded, as the tattoos may affect study findings due to altered light penetration or reflection. Subjects with Fitzpatrick skin types IV, V, and VI (darker skin phenotypes) and subjects who have participated in the “Phase 1 Study of LED-RL in Human Skin” (VA file number #15-12-00756) at the Sacramento VA Medical Center will be excluded.

Clinical Significance: The effects of visible light, while common in our environment (visible spectrum accounts for 44% of total solar energy), remain undefined. An important safety feature of visible red light (600 nm to 700 nm) is that it does not generate pro-carcinogenic DNA damage as does ultraviolet (UV) light. Recently

published clinical observations indicate that red light in combination with other modalities, such as photosensitizers in combined red light photodynamic therapy, can treat skin disease. However, preliminary in vitro data generated by our research group suggests that red light can function as a stand-alone treatment, eliminating the side-effects of chemical photosensitizers and the potential long-term harm of current UV phototherapy. Furthermore, commercially available light emitting diode-red light (LED-RL) units exist and are already FDA-cleared for other dermatological uses (such as rhytides and acne), thus clinical translation for use in skin diseases could occur relatively quickly following safety and efficacy demonstration. Currently, limited data exists pertaining to HF-LED-RL safety in different Fitzpatrick skin types. The uniqueness and importance of our study for medical science is that this will be the first clinical study of HF-LED-RL to evaluate the safety and regimen of these doses (480 and 640 J/cm2) in Fitzpatrick skin types I to III. Evaluating safety of HF-LED-RL phototherapy is important as HF-LED-RL may have the potential to treat skin diseases. To our knowledge, no clinical trials have been performed to determine the safety of HF-LED-RL in Fitzpatrick skin types I to III. Therefore, the innovation of this approach is that we intend to study the safety of HF-LED-RL modality in Fitzpatrick skin types I to III.

List of Abbreviations

HF-LED-RL, high fluence light-emitting diode-red light

MRSD, maximum recommended starting dose

MTD, maximum tolerated dose

UV, ultraviolet

Definitions

Fitzpatrick Skin Types: A method to categorize a person's skin based on his/her skin's reaction to sun or ultraviolet light exposure (Table 1).(Fitzpatrick 1988) It ranges from type I (always burn, never tan) to type VI (never burn, always tan). In general, Caucasian or white skin color is considered Fitzpatrick skin types I, II, and III, while darker skin colors are considered Fitzpatrick skin types IV, V, and VI.

Table 1. Skin type and sunburn sensitivity (Fitzpatrick Classification) (Fitzpatrick 1988)

Fitzpatrick Skin Type	**Response to Sun Exposure**	**Basic Skin Color**
I	Always sunburns, never tans	Pale white
II	Sunburns easily, develops a light Tan	White
III	Sunburns moderately, develops a moderate tan	White
IV	Sunburns minimally to rarely, develops a deep tan	Light brown/olive
V	Never sunburns, develops a dark tan	Brown
VI	Never sunburns, no noticeable change in skin color	Black

Contents

Protocol Title: EBIRE: Phase I Study of High Fluence LED-Red Light in Fitzpatrick Skin Types I to III

1.0 Study Personnel

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2.0 Introduction

- The effects of visible light, while common in our environment (visible spectrum accounts for 44% of total solar energy), remain undefined. An important safety feature of visible red light (600 nm to 700 nm) is that it does not generate pro-carcinogenic DNA damage as does ultraviolet (UV) light. Recently published clinical observations indicate that red light in combination with other modalities such as photosensitizers in combined red light photodynamic therapy can treat skin diseases. However, preliminary in vitro data generated by our research group suggests that red light can function as a stand-alone treatment, eliminating the side-effects of chemical photosensitizers and the potential long-term harm of current UV therapy. Furthermore, commercially available light emitting diode-red light (LED-RL) units exist and are already FDA-cleared for other dermatological uses (such as rhytides and acne), thus clinical translation for use in skin diseases could occur relatively quickly following safety and efficacy demonstration.
- We do not classify erythema (redness) lasting less than 24 hours as an adverse event in our study. Erythema is a common expected outcome that

may occur in at least 10% of subjects as previously demonstrated in published studies.(Sadick 2008, Sadick 2008) Common expected procedure outcomes include: warmth, erythema (redness), and edema (swelling) that is expected to last less than 24 hours. To our knowledge, there are no animal studies that have utilized this device (Omnilux new-U) at these doses (480 and 640 J/cm2). This device has a FDA 510K clearance, is sold for home use, and is generally regarded as safe in humans.

- In a randomized, controlled, dose escalation Phase I study of LED-RL in Human Skin (VA file 15-12-00756) conducted by our research group (hereinafter referred to as “previous Phase 1 LED-RL study”), we studied HF-LED-RL at doses of 160 J/cm2, 320 J/cm2, and 480 J/cm2 in all Fitzpatrick skin types. The maximum recommended starting dose (MRSD) of 160 J/cm2 is based upon previously published maximum doses of LED-RL phototherapy used in clinical studies that demonstrated clinical safety with no adverse events. (Sadick 2008, Sadick 2008). In the “previous Phase 1 LED-RL study”, the MRSD (160 J/cm2) was administered to Group 1 and the dose was escalated in subsequent groups using the classical method for dose escalation as described by Spilker: starting with dose (X) increased by an equal amount (in this instance: X=160 J/cm2, 2X=320 J/cm2, 3X=480 J/cm2, 4X=640 J/cm2). We demonstrated that the maximum tolerated dose (MTD) for HF-LED-RL was 320 J/cm2 in the “previous Phase 1 LED-RL study” based on an adverse event of a blister in one male subject with Fitzpatrick skin type V with HF-LED-RL at fluence of 480 J/cm2 (unpublished

data). The other two subjects, who were of Fitzpatrick skin types I to III, treated with HF-LED-RL at fluence of 480 J/cm2 had no adverse event.

48 subjects had no response or adverse event to any dose of HF-LED-RL or mock therapy. Eleven subjects had an expected, anticipated adverse event: One subject had faint erythema/redness that resolved after approximately one day (less than 48 hours) and ten subjects had transient post-inflammatory hyperpigmentation (PIH), which is mild tanning.

- Currently, limited data exists pertaining to HF-LED-RL safety in different Fitzpatrick skin types. Fitzpatrick skin types is a method to categorize skin types based on their reaction to sun or ultraviolet light exposure.(Fitzpatrick 1988) It ranges from type I (always burn, never tan) to type VI (never burn, always tan). In general, Caucasian (white) skin types are considered Fitzpatrick skin types I, II, or III while darker skin types are considered Fitzpatrick skin types IV, V, or VI. In the “previous Phase 1 LED-RL Study”, we did not evaluate or record Fitzpatrick skin types, but we recorded data for race and ethnicity based on National Institutes of Health (NIH) guidelines. Ethnicity and race corresponds closely with Fitzpatrick skin types as Caucasian skin types are Fitzpatrick skin types I to III and ethnic people are Fitzpatrick skin types IV to VI. Therefore, Fitzpatrick skin types scoring of subjects listed in ‘Part 1’ was based on race and ethnicity.
- We demonstrated in the “previous Phase 1 LED-RL study” that darker skin phenotypes (Fitzpatrick skin types IV, V, and VI) are more photosensitive to visible red light, as evident by an adverse event of a blister in one study

subject with Fitzpatrick skin type V at 480 J/cm2 HF-LED-RL. The other two subjects, who were of Fitzpatrick skin types I to III, treated with HF-LED-RL at fluence of 480 J/cm2 had no adverse event. Therefore, we wanted to explore the safety of HF-LED-RL at doses of 480 J/cm2 and 640 J/cm2 in Fitzpatrick skin types I to III. This finding that skin of color subjects may be more photosensitive to HF-LED-RL than Caucasian subjects is significant to the scientific community because we demonstrated that Fitzpatrick skin types respond to visible red light differently than to ultraviolet light. Darker skin (Fitzpatrick skin types IV to VI) is photoprotective for ultraviolet wavelengths, but more photosensitive to HF-LED-RL than subjects with light skin (Fitzpatrick skin types I to III). This photosensitivity may be due to increased skin pigment melanin which absorbs visible light. This hypothesis is supported by and corresponds to clinical observations with the use of visible light laser therapy in patients with skin of color. Therefore, this study will investigate the differential effects of HF-LED-RL on Fitzpatrick skin types I to III.

- This Phase 1 study (Storer 1989 – Phase 1 study design) will establish the safety of HF-LED-RL up to 640 J/cm2 in human skin in this population of Fitzpatrick skin types I, II, and III. The results of this phase I study may establish differential safety of HF-LED-RL in Fitzpatrick skin types, which would determine dose stratification and treatment parameters for future clinical studies that use HF-LED-RL as a therapeutic modality. It may also determine what dose of HF-LED-RL is safe to use in Fitzpatrick skin types I

to III. Upon successful demonstration of safety of HF-LED-RL in Fitzpatrick skin types I to III, future phase II studies may reference our phase I safety data to perform efficacy studies of HF-LED-RL in human skin for treatment of skin diseases. The uniqueness and importance of our study for medical science is that this will be the first study of HF-LED-RL in humans with Fitzpatrick skin types I to III to evaluate the safety and regimen of these doses (480 and 640 J/cm2). Evaluating safety of HF-LED-RL phototherapy is important as HF-LED-RL may have the potential to treat skin diseases. To our knowledge, no clinical trials have been performed to determine the safety of HF-LED-RL in Fitzpatrick skin types I to III. Therefore, the innovation of this approach is that we intend to study the safety of HF-LED-RL modality in Fitzpatrick skin types I to III.

- This randomized, controlled Phase 1 clinical study requires a study temperature-matched control, which is the mock therapy device. The mock therapy will serve as a control and help evaluate if side effects are due to HF-LED-RL light or the heat output that is emitted from the study device. If an adverse event occurs with the HF-LED-RL device only, then the HF-LED-RL light may have caused the adverse event. If an adverse event occurs with the mock device only, then the adverse event may have been caused by the heat output. However, if the same adverse event occurs with both HF-LED-RL and mock therapy at the same time duration, then the adverse event may have been caused by the heat output generated from both HF-LED-RL and mock devices.

- Potential subjects who are willing and eligible for the study will be recruited from the Sacramento VA Medical Center, Mather. No vulnerable populations will be recruited to this study. Subjects with Fitzpatrick skin types IV, V, and VI will be excluded because the MTD for subjects with Fitzpatrick skin types IV, V, and VI was established in the “previous Phase 1 LED-RL study” as 320 J/cm2 HF-LED-RL due to an adverse event of a blister in one study subject with Fitzpatrick skin type V at 480 J/cm2 HF-LED-RL. No subsequent testing of 480 J/cm2 was performed in subjects with Fitzpatrick skin types IV, V, and VI due to the study design of the “previous Phase 1 LED-RL study” where if any adverse event occurred, further testing at that dose would be discontinued. In this study, we will not test higher fluences of 480 J/cm2 and 640 J/cm2 in subjects with Fitzpatrick skin types IV, V, and VI. Subjects who have previously participated in the “previous Phase 1 LED-RL study” will be excluded to maintain unbiased results.

3.0 Objectives

- The purpose of this study is to determine the safety of HF-LED-RL phototherapy in Fitzpatrick skin types I to III.
- We hypothesize that HF-LED-RL phototherapy at fluences of 480 J/cm2 may be safe in subjects with Fitzpatrick skin types I to III. We hypothesize that HF-LED-RL phototherapy at fluence of 640 J/cm2 may be safe in subjects with Fitzpatrick skin types I to III.

4.0 Resources and Personnel

- Location: Building 801, Dermatology Service, Sacramento VA, Mather, CA
- Personnel: Jared Jagdeo, MD, MS (Attending Dermatologist, PI); Erica Wang, MD (Research Coordinator); Ramanjot Kaur, MD (Research Coordinator)
- Dr. Jagdeo, Dr. Wang, and Dr. Kaur will have access to protected health information and will be involved in recruiting subjects, obtaining informed consent, administering survey/interview procedures, and performing data analysis.

5.0 Study Procedures

5.1 Study Design

- This is a single-blind, randomized, ascending dose escalation Phase I study of HF-LED-RL in healthy subjects with Fitzpatrick skin types I to III to evaluate safety of HF-LED-RL in Fitzpatrick skin types I to III (Figure 1). The study endpoint of 640 J/cm2 is due to feasibility, as this dose corresponds to two hours of HF-LED-RL irradiation, and we anticipate decreased subject compliance with HF-LED-RL exposures longer than 2 hours in duration. The study endpoint of 640 J/cm2 was also selected as this dose demonstrated increased anti-fibrotic properties in vitro compared to lower doses of HF-LED-RL (Mamalis 2015). Subjects will receive HF-LED-RL phototherapy or mock therapy three times a week for

three consecutive weeks, which is a standard phototherapy regimen based on phototherapy guidelines (Anderson et al 2015, Menter et al 2010, Zanolli et al 2004).

The HF-LED-RL light source is a commercially available Omnilux New-U hand-held LED-RL phototherapy unit (provided by Photo Therapeutics, Carlsbad, CA, USA), and is FDA-cleared for treatment of periorbital rhytides (crow's feet) with doses up to 160 J/cm2. The temperature-matched mock therapy unit, also provided by Photo Therapeutics, Carlsbad, CA, USA, generates only heat output comparable to heat generated by the HF-LED-RL device, which is less than two degrees Celsius of heat output, and does not emit HF-LED-RL.

We do not classify erythema (redness) lasting less than 24 hours as an adverse event in our study, and is expected to occur in at least 10% of subjects as previously demonstrated in published studies (Sadick 2008, Sadick 2008). Common expected procedure outcomes include: warmth, erythema (redness), and edema (swelling) that is expected to last less than 24 hours.

- The maximum tolerated dose (MTD) is defined as the dose level below the dose producing unacceptable but reversible toxicity in two or more subjects ($\geq$20%) and is considered the upper limit of subject tolerance. If two or more subjects experiences any adverse event (including: first-degree or higher skin burning or blistering, erythema lasting more than 24 hours, swelling, pain, ulceration, infection, change in sensation, and/or

muscle weakness), then this is the dose one above the MTD and we will not proceed with this dose or escalate the dose. The dose below the dose that generated the adverse event is the MTD. Rare but serious adverse events include second or higher degree skin burn, severe swelling, pain, ulceration, change in sensation, or muscle weakness leading to hospitalization, life-threatening events, or death.

The data safety monitoring board (DSMB) includes: Dr. Rivkah Isseroff, Dr. Samuel Hwang, and Dr. Emanual Maverakis

HF-LED-RL phototherapy and mock therapy at fluences of 480 J/cm2 or 640 J/cm2 will be administered to 65 subjects with Caucasian (white) skin types (Fitzpatrick skin types I, II, and III) to determine safety of HF-LED-RL at fluences of 480 J/cm2 and 640 J/cm2 in Fitzpatrick skin types I, II, and III. Because up to 320 J/cm2 HF-LED-RL was found to be safe in all Fitzpatrick skin types (unpublished data from “previous Phase 1 LED-RL study”), this study will study 480 J/cm2 and 640 J/cm2 in Fitzpatrick skin types I, II, and III based on Spilker’s dose escalation protocol (X=160 J/cm2, 2X=320 J/cm2, 3X = 480 J/cm2, and 4X = 640 J/cm2).

Number of subjects in each group:

Group 1 (480 J/cm2; 3 or 6 HF-LED-RL phototherapy subjects and 2 or 4 mock therapy subjects) - Total 5 or 10 subjects

Group 2 (640 J/cm2; 3 or 6 HF-LED-RL phototherapy subjects and 2 or 4 mock therapy subjects) - Total 5 or 10 subjects

Group 3 (480 or 640 J/cm2 depending on dose escalation algorithm; 27 HF-LED-RL phototherapy subjects and 18 mock therapy subjects) - Total 45 subjects

* If there is one adverse event in one subject in either Group 1 or 2, five additional subjects will be added to that group (3 will receive HF-LED-RL and 2 will receive mock therapy).

We based our dose escalation protocol for this new study on a similar Phase 1 dose escalation study design outlined in the Journal of National Cancer Institute (Le Tourneau et al 2009), to determine dose escalation and to account for a possible outlier effect in the treatment group. Dose escalation starts at fluence of 480 J/cm2 and continues up to fluence of 640 J/cm2 until at least two subjects among a cohort of five to ten subjects experience an adverse event (i.e. ≥20% of subjects with an adverse event at that dose level).

Our dose-escalation protocol is as follows (Figure 2): In the first group (Group 1), HF-LED-RL phototherapy or mock therapy treatment time durations associated with 480 J/cm2 will be administered to five subjects. Five subjects will be enrolled with three subjects randomized to HF-LED-RL phototherapy and two subjects randomized to mock therapy. Randomization is performed with website: www.randomizer.org. The randomizer will generate arabic numerals (e.g. “1”, “2,” “3”). Each enrolled subject will undergo two randomizations. For the first randomization, “1” is Group 1, “2” is “Group 2” and “3” is Group 3. 10 subjects will be

randomized to Group 1, 10 subjects will be randomized to Group 2, and 45 subjects will be randomized to Group 3. If there are no adverse events in the first five subjects of either Group 1 or 2, then the remaining 5 subjects of the 10 subjects randomized to that group will default into Group 3. For the second randomization, "1" is HF-LED-RL phototherapy and "2" is mock therapy. This study is single-blind and subjects will be blinded to this randomization, while researchers (Dr. Jagdeo, Dr. Wang, and Dr. Kaur) have knowledge of all subjects' randomization for the entirety of this study.

Dose escalation starts at fluence of 480 J/cm2 and continues up to fluence of 640 J/cm2 until at least two subjects among a cohort of five to ten subjects experience an adverse event (i.e. $\geq$20% of subjects with an adverse event at that dose level). If there are no adverse events in the five subjects treated with HF-LED-RL or mock therapy at fluence of 480 J/cm2 in Group 1, then we will escalate the dose of HF-LED-RL or mock therapy to fluence of 640 J/cm2 in the next cohort of five subjects (Group 2). If there is a single adverse event with HF-LED-RL or mock therapy at fluence of 480 J/cm2, we will repeat the same dose of 480 J/cm2 in a new cohort of five additional subjects (Group 1A). This is to account for a possible outlier effect. If two or more subjects in the first cohort of Group 1 experiences an adverse event with HF-LED-RL or mock therapy at fluence of 480 J/cm2, then the study will stop and the MTD is 320 J/cm2. If there are no adverse events in Group 1A, then the dose will be escalated to 640

J/cm2 in the next cohort (Group 2). If there is an adverse event in Group 1A (≥20%), then the study will stop and the MTD is 320 J/cm2.

After either a MTD has been established or the study endpoint of 640 J/cm2 has been achieved, an additional 27 HF-LED-RL phototherapy subjects (for a total of 30 or 33) and 18 mock therapy (for a total of 20 or 22) (determined randomly) will be enrolled to satisfy Hanley's Rule of Three, such that it can be concluded with 95% confidence that fewer than 1 person in 10 will experience an adverse event (Figure 3). (Hanley 1983) If the MTD is 320 J/cm2, then the study will be stopped and no further testing of the MTD of 320 J/cm2 in the larger cohort will be indicated because the MTD of 320 J/cm2 was already tested in a large cohort in the "previous Phase 1 LED-RL study". Of the larger expansion cohort, the study will be halted (stopped) if adverse events determined to be device related equals or exceeds 30%.

This clinical trial will be registered on https://clinicaltrials.gov following IRB approval and prior to subject enrollment.

- The subject will receive standard of care treatment in the dermatology clinic for any adverse event. Physical examination/visual inspection of the treated forearm will occur at every study visit. Treatment will be initiated, if indicated, for any procedural outcomes or adverse events noted at every study visit. Any general dermatology adverse events will be managed by Dr. Jagdeo in the Dermatology clinic, per standard of care. If a skin ulcer occurs, we will record the skin ulceration as a superficial ulceration

(meaning it is nearly flush with the skin) or, if measurable, the depth of ulceration in millimeters. If skin ulceration occurs, we will consult Dr. Rivkah Isseroff, who is an expert in wound healing and head of the Sacramento VA wound clinic, for management. If change in sensation or muscle weakness occurs in a subject, the subject will be sent to Sacramento VA Emergency Room for urgent grading and management. If there are any other adverse events that cannot be managed in the Dermatology clinic, the subject will be sent to the Sacramento VA Emergency Room for urgent care.

- All procedures will occur in the Dermatology clinic at the Sacramento VA Medical Center (observed by Dr. Jagdeo, Dr. Wang, and/or Dr. Kaur), three times per week for three consecutive weeks for total of nine study visits. Subjects will be counseled regarding common expected procedure outcomes including warmth, erythema (redness) and edema (swelling), found to resolve within 24 hours in other studies. (Sadick 2008) Any adverse events that occur in office during or immediately after HF-LED-RL phototherapy or mock therapy session will be recorded by Dr. Jagdeo. Subjects will be called on Mondays to serve as a reminder of upcoming study visits for the week.
- Subjects will record daily any adverse events that occur at home using a subject diary of adverse events. The study diary will be completed approximately every 24 hours from the time of completion of the study procedure. The subject diary will have instructions on the first page and a

chart on other pages for the subject to complete for every symptom noted at home (attached as separate document). The chart will have headers of ‘Date,’ ‘Time Symptom Started,’ ‘Time Symptom Cleared,’ ‘Location,’ ‘Describe the Symptom,’ ‘Severity,’ ‘Things that Make it Better,’ ‘Things that Make it Worse,’ ‘Any Treatments Tried at Home,’ and ‘MD Initial’. If a subject notices any changes sooner than 24 hours, they are encouraged to note it in their subject diary as soon as possible. If there are no changes, subjects will write “There are no changes.” Recording in a diary should take 0 minutes per day if there is no reportable change. It may take up to 3 minutes per day if there is a reportable change. If there are any reportable changes, subjects will describe reportable changes using the provided instructions and template. Prior to study procedure at every study visit, subjects will be asked about any adverse events that have occurred, including, but not limited to: erythema, blisters, swelling, pain, ulceration, infection, numbness, tingling, and weakness. Subject’s diaries will also be reviewed prior to study procedure at every study visit. Dr. Jagdeo, Dr. Wang, or Dr. Kaur will initial in the ‘MD Initial’ area at every visit, certifying that one of the researchers has reviewed the subject diary at every study visit.

Study Timeline:
HF-LED-RL Phototherapy or mock therapy procedure times are as follows:
Group 1 (480 J/cm2; 3 or 6 HF-LED-RL phototherapy subjects and 2 or 4 mock therapy subjects) - 90 minutes
Group 2 (640 J/cm2; 3 or 6 HF-LED-RL phototherapy subjects and 2 or 4 mock therapy subjects) - 120 minutes

Group 3 (480 J/cm2 or 640 J/cm2 based on dose escalation algorithm; 27 HF-LED-RL phototherapy subjects and 18 mock therapy subjects) – 90 or 120 minutes
* If there is one adverse event in one subject in either Group 1 or 2, five additional subjects will be added to that group (3 will receive HF-LED-RL and 2 will receive mock therapy).

Sample Timeline *Please see above list for procedure times for Groups 1, 2, and 3.

Week 0: (All subjects will be tested for photosensitivity with 20 minutes and 106.7 J/cm2 of HF-LED-RL)

Visit 1

Screening and obtaining informed consent (10 minutes) Subject can return at a later date to sign the informed consent if he or she desires to review the consent form in more detail.
Physical examination of nondominant forearm, pre-procedure photograph (5 minutes)
Procedure for testing photosensitivity – HF-LED-RL phototherapy on nondominant upper forearm (20 minutes, 106.7 J/cm2)
Post-procedure photograph (5 minutes)

Visit 2 (24 hours after Visit 1)

Physical examination of nondominant forearm for photosensitivity which includes warmth, erythema (redness), edema (swelling), rash, pain, sensory changes, muscle weakness, or discomfort lasting more than 24 hours (10 minutes)
Photograph (5 minutes)
Subjects who are photosensitive will be excluded from this study. Subjects who are not photosensitive will proceed with study protocol.

Week 1:

Monday (**Visit 3**)
Physical examination of nondominant forearm, pre-procedure photograph (5 minutes)
Procedure (Refer to above for procedure duration)
Post-procedure photograph (5 minutes)

Wednesday (**Visit 4**)
Physical examination of nondominant forearm, pre-procedure photograph, and review of subject diary of adverse events (5 minutes)
Procedure (Refer to above for procedure duration)
Post-procedure photograph (5 minutes)

Friday (**Visit 5**)
Physical examination of nondominant forearm, pre-procedure photograph, and review of subject diary of adverse events (5 minutes)

Procedure (Refer to above for procedure duration)
Post-procedure photograph (5 minutes)

Week 2:
Monday (**Visit 6**)
Physical examination of nondominant forearm, pre-procedure photograph, and review of subject diary of adverse events (5 minutes)
Procedure (Refer to above for procedure duration)
Post-procedure photograph (5 minutes)

Wednesday (**Visit 7**)
Physical examination of nondominant forearm, pre-procedure photograph, and review of subject diary of adverse events (5 minutes)
Procedure (Refer to above for procedure duration)
Post-procedure photograph (5 minutes)

Friday (**Visit 8**)
Physical examination of nondominant forearm, pre-procedure photograph, and review of subject diary of adverse events (5 minutes)
Procedure (Refer to above for procedure duration)
Post-procedure photograph (5 minutes)

Week 3:
Monday (**Visit 9**)
Physical examination of nondominant forearm, pre-procedure photograph, and review of subject diary of adverse events (5 minutes)
Procedure (Refer to above for procedure duration)
Post-procedure photograph (5 minutes)

Wednesday (**Visit 10**)
Physical examination of nondominant forearm, pre-procedure photograph, and review of subject diary of adverse events (5 minutes)
Procedure (Refer to above for procedure duration)
Post-procedure photograph (5 minutes)

Friday (**Visit 11**)
Physical examination of nondominant forearm, pre-procedure photograph, and review of subject diary of adverse events (5 minutes)
Procedure (Refer to above for procedure duration)
Post-procedure photograph (5 minutes)

Average length of study visits for: Group 1 - 100 minutes, Group 2 - 130 minutes,

Group 3 – 100 or 130 minutes based on dose escalation algorithm.

Detailed Procedure: Intervention — Subject will be inside a private clinic exam room. The subject's nondominant proximal anterior forearm will be examined and cleaned with alcohol pads, A surgical marking pen will be used to mark three points to outline the procedure area at the start and completion of every session to ensure reproducible placement of the device. The HF-LED-RL phototherapy or mock therapy hand-held unit will be held in place and in direct contact with the cleaned area using non-adhesive tape (ACE elastic bandage or similar) during the procedure. Protective eyewear will be provided for all subjects to use at HF-LED-RL phototherapy and mock therapy sessions. Dr. Jagdeo, Dr. Wang, or Dr. Kaur will be observing the procedure and assessing for any safety issues during and immediately post-procedure. Treatment will be started, if indicated, for any adverse events noted during physical examination at each study visit.

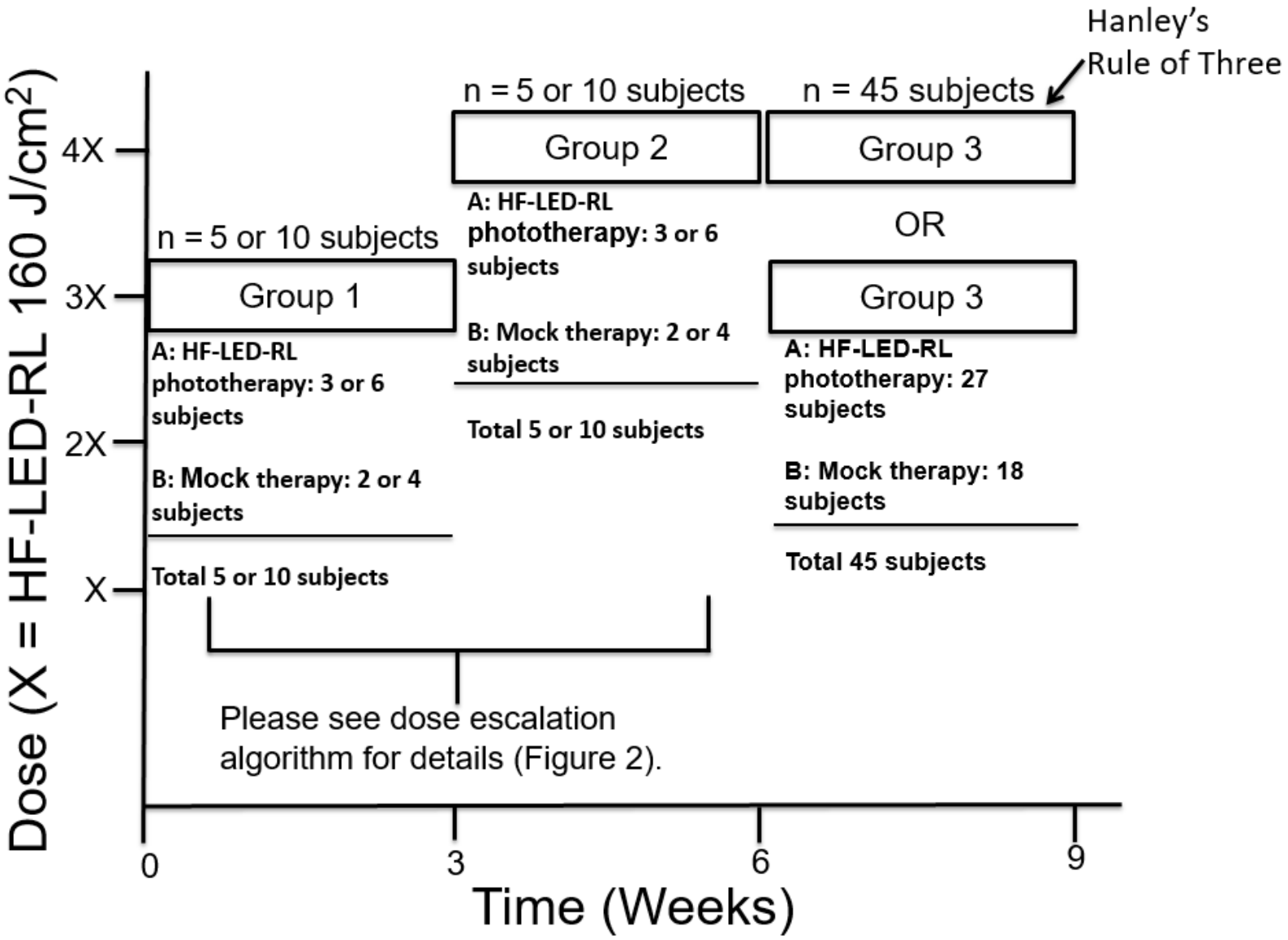

Figure 1. Schematic of study design.

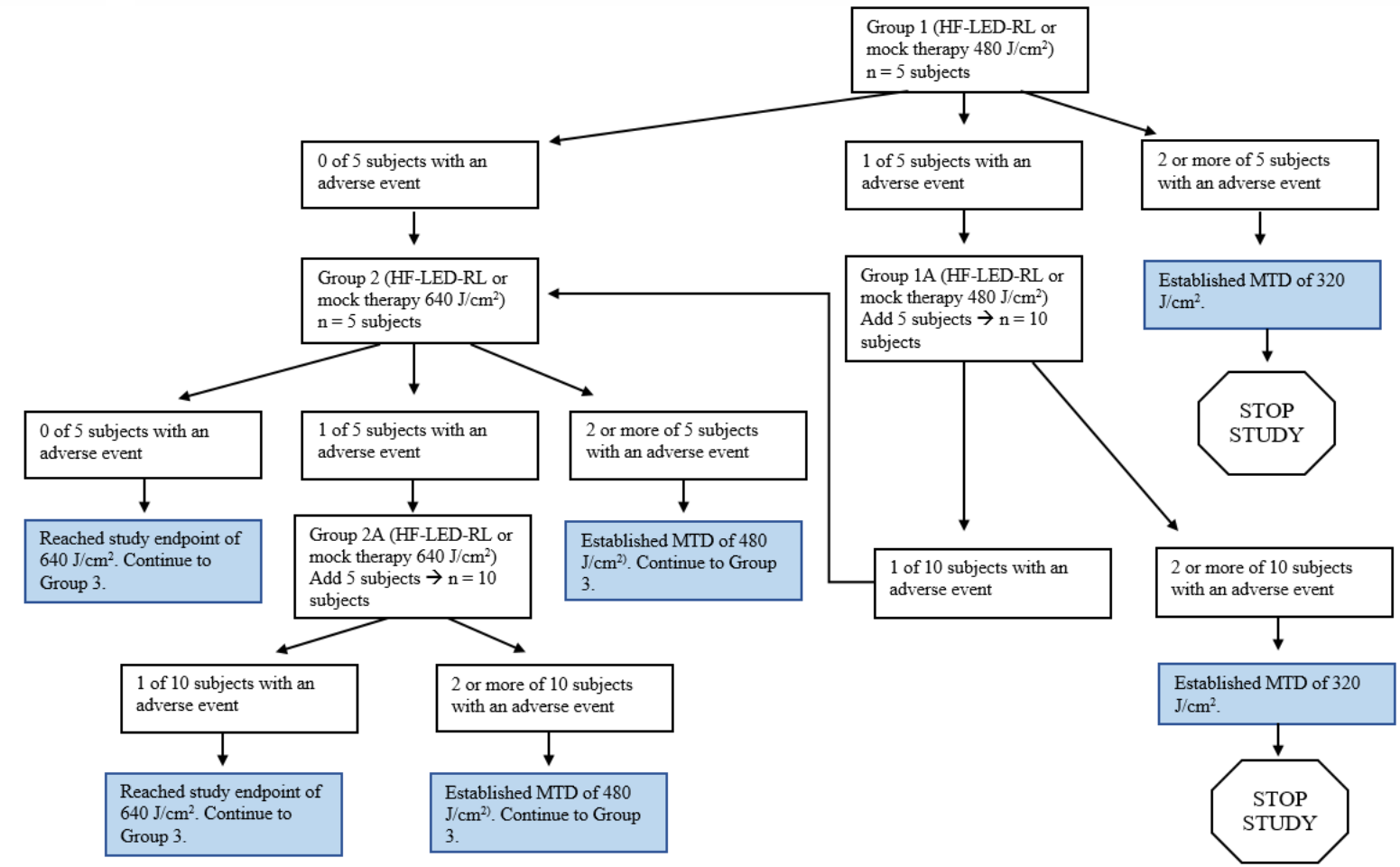

Figure 2. Dose escalation algorithm.

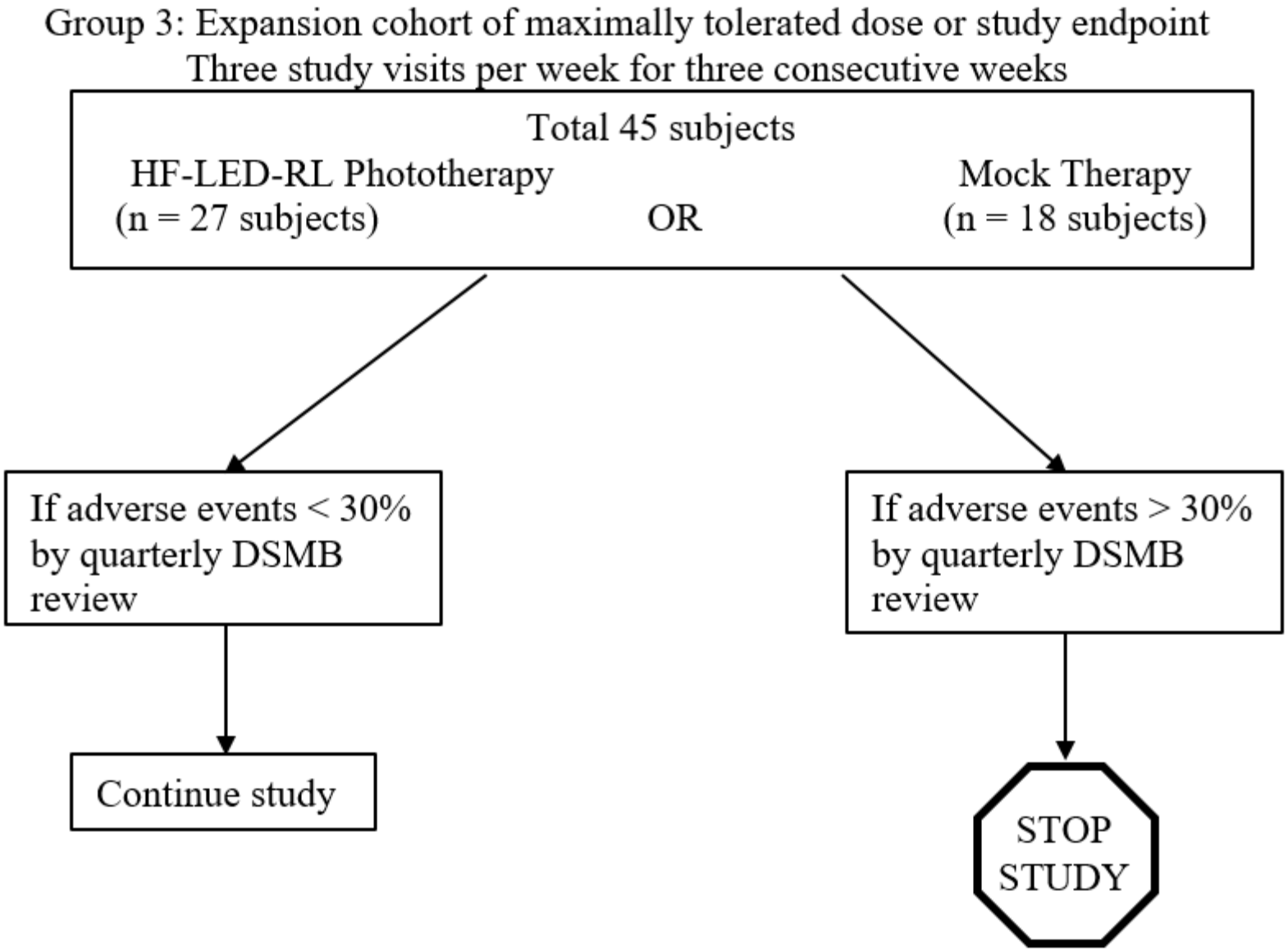

Figure 3. Expansion cohort design.

- Subjects who receive HF-LED-RL phototherapy may have a greater risk compared to subjects who receive mock therapy. However, all subjects are closely monitored by Dr. Jagdeo, Dr. Wang, and/or Dr. Kaur three times per week for three consecutive weeks at each study visit and by review of subject's diary of adverse events. All safety precautions, including sanitizing equipment and goggles with Sani-Wipe before each study subject use, requiring subjects to use safety googles during each session, and verifying subject identity, study procedure site of left or right forearm, and correct dose of HF-LED-RL or mock therapy, will be taken. All adverse events will be documented and if necessary, reported to the IRB.

  All HF-LED-RL phototherapy and mock therapy hand-held units will be cleaned with anti-germicidal wipes before and after each procedure. All subjects' nondominant proximal anterior forearm will be cleaned with alcohol wipes prior to placement of HF-LED-RL phototherapy or mock therapy unit. All subjects will be provided with protective eyewear during all procedures. The study procedure will occur on the subject's nondominant proximal anterior forearm, with a surgical marking pen to mark three points to outline the procedure area at the start and completion of every session to ensure reproducible placement of the device. Subjects will be asked which hand is dominant or preferred when writing. Subjects can report being left-handed, right-handed, or ambidextrous. Subjects who are ambidextrous may identify their preferred nondominant forearm for the

study procedure to Principal Investigator (Dr. Jared Jagdeo) or study coordinators (Dr. Wang and Dr. Kaur) prior to start of study.

In addition to the aforementioned precautions to minimize risks, all subjects will be screened by Dr. Jagdeo, Dr. Wang, and/or Dr. Kaur by reviewing their medical records and performing a physical examination after obtaining informed consent. Dr. Jagdeo, Dr. Wang, and/or Dr. Kaur will be present during HF-LED-RL phototherapy or mock therapy procedures, and observe and document any common expected procedure outcomes and adverse events. Any adverse event experienced by the subject will be evaluated and treated according to the standard of care. The study subjects have direct contact information (phone numbers and email addresses) of Dr. Wang, and Dr. Wang may be reached at any time.

The Omnilux New-U hand-held HF-LED-RL phototherapy unit is commercially available and FDA-cleared for treatment of periorbital rhytides (crow's feet) with doses up to 160 J/cm2. We do not expect the risk of using HF-LED-RL phototherapy or mock therapy in our current study will be any different from the current FDA-cleared indication.

- Potential subjects will be recruited from the Sacramento VA Medical Center, Mather, and any subjects who are willing and eligible for the study will be invited to participate. The total number of participants approved for recruitment is 200.

5.2 Recruitment Methods

- The total number of participants approved for recruitment is 200.
- Potential subjects will be identified and recruited from the Sacramento VA Medical Center, Mather via discussion with Dr. Jagdeo, Dr. Wang, and/or Dr. Kaur in Dermatology Clinic or through subject interest from IRB-approved flyers posted at the Sacramento VA Medical Center.
- Flyer (Please see below and as separate attachment)

Inviting Veterans to Participate in a Clinical Trial Studying the Safety of Red Light On Skin!

The Dermatology Service is exploring the safety of a FDA-cleared red light device. To study the safety of red light, we are evaluating different treatment times using the device in healthy skin over a three-week period. We previously studied the safety of light in all skin types and this study is designed to investigate the effects of light on fair skinned individuals.

Would you like to:

- Help veterans and the population at large?
- Make a contribution to medical science?
- Help discover new treatments for skin disease?
- Get compensated for your time participating in this study?

PLEASE ASK US!

Who may participate?

- Veterans of any age, with Caucasian (white) skin that may burn easily.
- Veterans who have not participated in a Sacramento VA red light study previously.
- Veterans wanting to make a positive impact on others.

Where is this study?

- Building 801, Dermatology Clinic, Sacramento VA Medical Center, Mather

If you are interested in participating in this study or if you have any questions, please contact research coordinator:

Erica Wang, MD
Phone: (808)428-7082

VA | U.S. Department of Veterans Affairs

- Subjects will receive a prorated amount of compensation based upon the number of completed study visits. Subjects must complete two or three study visits in the week to receive payment for that week. If patients complete two study visits in a week, they will receive a prorated payment of $33.33 for that week. If a subject completes three study visits in a week, they will receive a payment of $50 for that week. Completion of week 1: $50, week 2: $50, and week 3: $50. Patients will receive a check weekly and there will be no delay in receiving the payment. If a subject misses two or more study visits total, he/she will be discontinued from the study.

5.3 Informed Consent Procedures

- Informed consent will be obtained using IRB-approved informed consent forms.
- Informed consent will by obtained by Dr. Jagdeo, Dr. Wang, or Dr. Kaur. No persons with impaired decision-making capacity will be recruited to this study. Dr. Jagdeo, Dr. Wang, and/or Dr. Kaur will determine whether the potential subject has decision-making capacity via conversational interaction with the potential subject.
- Dr. Jagdeo, Dr. Wang, and Dr. Kaur has completed the CITI Human Research Subject training and has the knowledge and understanding of the clinical trial to obtain and document informed consent and explain the study to the subjects.

5.4 Inclusion/Exclusion Criteria

Inclusion Criteria:

1) Healthy subjects, any sex, ethnicity, and age with Fitzpatrick skin types I, II, or III that do not meet exclusion criteria. Fitzpatrick skin types will be determined based on NIH's race/ethnicity categories. Fitzpatrick skin types I to III will be persons who are Caucasian or white. NIH defines "White" as "A person having origins in any of the original peoples of Europe, the Middle East, or North Africa." A subject's Fitzpatrick skin

type, whether they are Fitzpatrick skin type I or II or III, will not be documented.

2) Nondominant proximal anterior forearm is wide enough to ensure reproducible placement of HF-LED-RL phototherapy or mock therapy hand-held unit
3) Available and willing to attend all study visits
4) Able and willing to give informed consent

Exclusion Criteria:

1) Subjects with Fitzpatrick skin types IV, V, or VI
2) Subjects on any photosensitizing medications (e.g. lithium, melatonin, phenothiazine antipsychotics, antibiotics)
3) Subjects with light-sensitive conditions (Based on medical chart review, self-reporting, or failing the 20 minutes at fluence of 106.7 J/cm2 photosensitivity evaluation)
4) Subjects with diabetes mellitus (DM) (Based on medical chart review or self-reporting). Subjects with DM may have a higher risk of longer wound healing time.
5) Subjects with a history of skin cancer: basal cell carcinoma (BCC), squamous cell carcinoma (SCC), or melanoma
6) Subjects with systemic lupus erythematous (SLE)
7) Subjects with open wounds on the nondominant proximal anterior forearm
8) Subjects with fibrotic skin disease or other skin conditions on the nondominant proximal anterior forearm
9) Subjects with tattoos that cover the procedure site on the nondominant proximal anterior forearm
10) Subjects who previously participated in the Phase 1 study of LED-RL in Human Skin (VA file #15-12-00756)

5.5 Study Evaluations

- All subjects will be evaluated for photosensitivity (20 minutes with fluence of 106.7 J/cm2 of HF-LED-RL) prior to start of study procedures, as recommended by the manufacturer's user guide instructions. A 20-minute session of HF-LED-RL phototherapy will be performed on the subject's nondominant proximal anterior forearm, and evaluation for photosensitivity will occur 24 hours post HF-LED-RL phototherapy. Subjects will be excluded from the study if they fail the 20 minute photosensitivity evaluation or do not return for photosensitivity evaluation between 24-48 hours post HF-LED-RL photosensitivity testing. Criteria for failing the photosensitivity testing include but are not limited to: warmth, erythema (redness), edema (swelling), rash, pain, or discomfort lasting more than 24 hours. Subjects are required to complete a study diary and report any adverse events to Dr. Jagdeo, Dr. Wang, or Dr. Kaur.

5.6 Data Analysis

- Once all study subjects have finished all study procedures and data collection is complete, Dr. Jagdeo, Dr. Wang, and/or Dr. Kaur will then be performing the data analysis. Data analysis will include analysis of demographics (e.g. age, gender, ethnicity, race, Fitzpatrick skin type) in each cohort by HF-LED-RL or mock therapy dose, frequency of adverse events by HF-LED-RL or mock therapy

groups, mean duration of erythema, total duration of erythema, and subgroup analysis by demographics of adverse events. Self-reported outcomes of erythema duration are based on self-reporting from subject's diary.

5.7 Withdrawal of Subjects

- Subjects may be withdrawn from the research without their consent in the event of an adverse event that jeopardizes the subject's safety or subject's noncompliance (e.g. missing two or more study visits). In the event that subject's study participation has to be discontinued, the principal investigator will explain to the participant the reasons for termination.
- There are no consequences/penalties should a subject decide to withdraw from the research. The subject is encouraged to contact Dr. Wang for the end-of-study visit. End-of-study visit will include photograph of the treated forearm, physical examination of the treated forearm, and collection of the subject's study diary. Subjects will be instructed to notify their primary care physician or follow-up in Dermatology clinic if any questions or concerns arise after the end of the study.

6.0 Reporting

- All subjects will be seen by Dr. Jagdeo (Principal Investigator), Dr. Wang, or Dr. Kaur. Study subjects are followed by their regular physicians, so

they will continue to receive usual care. Dr. Jagdeo, Dr. Wang, or Dr. Kaur will review the study subject's safety parameters (including history and physical) after study enrollment.

Although this is a minimal risk study, Dr. Jagdeo, Dr. Wang, or Dr. Kaur will monitor study subjects for common expected procedure outcomes and adverse events during and immediately after HF-LED-RL phototherapy or mock therapy. Monitoring will occur by direct observation and review of subject diary of adverse events at all study visits.

Dr. Jagdeo (Principal Investigator) will promptly report any serious adverse events or unanticipated problems involving risks to study subjects in accordance with regulations: reportable adverse events arising from any of the study procedures will be submitted promptly to the IRB. Although they are not anticipated to occur, unanticipated problems (involving risks to subjects) or Serious Adverse Events (SAE) in subjects will be reported to the IRB within 5 working days of awareness of the event. Copies of reports should be received by the IRB no later than 15 calendar days after the event.

- Performance and Frequency of Safety Reviews

  Dr. Jagdeo (Principal Investigator) reports on the progress of the study on a quarterly basis at the DSMB meeting. Dr. Jagdeo (Principal Investigator) will monitor study progress, outcomes and subject safety, and may make recommendations on changes to the study protocol. Meetings regarding the performance and safety of this study will be held quarterly at the Dermatology Clinic Conference room. The DSMB will report to the IRB quarterly.

- Individuals who will perform the safety monitoring

  Rivkah Isseroff, MD (Chief, Dermatology Service)

  Samuel Hwang, MD (Chairperson, UC Davis Dermatology)

  Emanual Maverakis, MD (Associate Professor, UC Davis Dermatology)

7.0 Privacy and Confidentiality

- Dr. Jagdeo (Principal Investigator), Dr. Wang, and Dr. Kaur will have access to protected health information for the purpose of determining study eligibility, and for the performance of and collection of data associated with study related procedures.
- We will collect only the minimum amount of the study subject's protected health information required to complete our study. To protect privacy, we will inform potential subjects of the minimum amount of personal information that would be required of them in order to participate in our study. Subjects are advised of the type and extent of information to be collected at the start of the study. Subjects will be consented individually in a private clinic office or exam room.
- Electronic data are stored in the \\vhamacrchsmc\mac_research\JAGDEO_RESEARCH Server, and paper copies data are kept in a locked office in a locked research cabinet in Sacramento VA Medical Center, Building 801, Room 8. Data will be anonymized for statistical analysis, with new unique identifiers linked to

study subjects. Photographs of the forearm undergoing the intervention will be taken before and after each session. Photographs will be taken with a VA-provided and authorized camera. Photographs will be saved to the VISTA imaging component of CPRS as part of the subject's VA medical record. Files saved on the camera prior to upload will be deleted once uploaded to subject's CPRS file.

8.0 Communication Plan

- N/A

9.0 References

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