A pragmatic trial of home versus office based narrow band ultraviolet B phototherapy for the treatment of psoriasis

Short title: Light Treatment Effectiveness (LITE) Study

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List of Abbreviations

AE: Adverse Event
BSA: Body Surface Area
CI: Confidence Interval
CRCU: Clinical Research Computing Unit
CRF: Clinical Research Form
DLQI: Dermatology Life Quality Index
EC: Ethics Committee
eICF: Electronic Informed Consent Form
FDA: Federal Drug Administration
GEE: Generalized Estimating Equations
HIPAA: Health Insurance Portability and Accountability Act of 1996
HTE: Heterogeneity of Treatment Effect
IRB: Institutional Review Board
ICF: Informed Consent Form
ICH: International Conference on Harmonisation (ICH)
ITT: Intent to Treat
MCAR: Missing Completely at Random
MCID: Minimal Clinically Important Difference
MI: Multiple Imputation
MICE: Multiple Imputation via Chained Equation
NB - UVB: Narrowband – ultraviolet B
PASI: Psoriasis Area and Severity Index
PCORI: Patient Centered Outcomes Research Institute
PGA: Physician Global Assessment
PHI: Protected Health Information
PI: Principal Investigator
PsA: Psoriatic Arthritis
SAE: Serious Adverse Event
UV: Ultraviolet
UVB: Ultraviolet B

Study Summary

Title	A pragmatic trial of home versus office based narrow band ultraviolet B phototherapy for the treatment of psoriasis
Short Title	Light Treatment Effectiveness (LITE) Study
IRB Number	831323
Protocol Number	PCS-1608-35830
Phase	Phase 4
Methodology	Pragmatic, randomized, active comparator effectiveness study
Study Duration	Screening, recruitment, enrollment, and subject completion of the study is anticipated to occur over a period of 3 years. For each patient the time periods are as follows: Screening: 28 days or longer based on local practice standard of care Treatment period: 84 days Observation post treatment period: 84 days
Study Center(s)	Multi-center clinical trial with approximately 20-40 sites
Objectives	To compare the effectiveness, safety (tolerability), and duration of treatment response at 12 weeks of home versus office-based narrowband ultraviolet B phototherapy for the treatment of psoriasis
Number of Subjects	1050 Stratified by Fitzpatrick skin type (350 skin type I/II, 350 skin type III/IV, 350 Skin type V/VI)

Main Inclusion and Exclusion Criteria	Inclusion criteria: 1. Willing and able to provide informed consent (age 18+) or parental permission and assent (ages 12-17) 2. Age 12 or older 3. Plaque or guttate psoriasis predominantly located on trunk and/or extremities, with a physician global assessment average of >1.0, and considered a candidate for phototherapy 4. Patient is deemed willing and able to comply with either in-office or in-home phototherapy: a. In office: Able to travel about 3 times per week for 12 weeks from home, work and/or school during business hours of local site b. In home: Has space to accommodate home phototherapy unit and patient (or if 12-17, parent), willing and able to follow home phototherapy instructions 5. New or established patient in the practice Exclusion criteria: 1. Patients who are judged unable or unwilling to comply with either in office or in home phototherapy due to time, work, school, or other financial constraints 2. Patients judged unable to follow home phototherapy protocol due to failure to demonstrate understanding of the following: a. How to operate the phototherapy device b. How to follow the dosing protocol c. Requirement to wear protective eyewear and genital protection equipment 3. Patients with known history of lack of efficacy to phototherapy or treated with phototherapy 14 days prior to baseline visit 4. Psoriasis predominantly located on scalp, body folds, genitals, palms and/or soles or with a physician global assessment average of ≤ 1.0 5. Patients deemed unsafe to be treated with phototherapy: a. History of photosensitivity or autoimmune disease such as lupus or dermatomyositis which can be aggravated by ultraviolet radiation b. History of arsenic intake c. Unable to tolerate standing for required duration of treatment due to age or physical function d. History of melanoma or multiple non-melanoma skin cancers that in the opinion of the principal investigator contraindicates treatment with phototherapy 6. Clinical site deems the participant is ineligible for reason other than eligibility or screening criteria.
Comparator Device	Daavlin 7 series 3 panel narrow band phototherapy home units (have 8-12 bulbs and a smaller, flat surface with door, measuring 21” wide, 74.5” tall, and 23.5”). The unit will have a dosimetery controller, a UV sensor built in that measures the intensity of the light. This unit is a class II device with a FDA 510K indication for psoriasis, vitiligo and atopic dermatitis/eczema.
Duration of administration (if applicable)	Approximately three times per week x 12 weeks

Reference therapy	Office based narrow band phototherapy (units typically have at least 24 bulbs in a surround structure)
Statistical Methodology	The co-primary endpoints of this study will be: • Physician Global Assessment (PGA) score of clear/almost clear (at week 12 or the time of phototherapy discontinuation, whichever comes first) • Dermatology Life Quality Index (DLQI) score of ≤5 which corresponds to no to small impact of dermatologic disease on quality of life at week 12 Secondary outcomes include: • Physician measured body surface area (BSA) x PGA • Concomitant topical psoriasis treatment • Patient reported time spent on phototherapy • Patient reported time and cost associated with travel for phototherapy treatments • Phototherapy number and dose • Duration of treatment response during observation period
Safety Evaluations	The primary safety outcome is the proportion of patients reporting treatment-emergent adverse events. Treatment emergent adverse events include patient reported burns and their severity. We will also collect data on all Serious Adverse Events whether treatment related or not.
Data and Safety Monitoring Plan	The local investigators are responsible for monitoring patient safety as per standard of care. Data quality will be monitored by the study Principal Investigator and his team centrally with queries and auditing of sites as necessary.

BACKGROUND AND STUDY RATIONALE

This study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56, and Good Clinical Practice: Consolidated Guidelines approved by the International Conference on Harmonisation (ICH).

Narrow band ultraviolet B (NB-UVB) phototherapy is a first line standard of care treatment for psoriasis. While being highly preferred by providers and patients its use is limited by inconvenience as patients must travel to the provider's office about 3 times per week for 12 weeks. Home phototherapy is an accepted alternative but relatively limited data in the U.S. has led to decisional uncertainty and thus wide variation in insurance coverage and utilization by physicians. We will therefore conduct a large pragmatic trial of home vs. office based phototherapy for the treatment of psoriasis. A pragmatic trial aims to reflect real world clinical practice as closely as possible and therefore provides the best estimates of effectiveness, or generalizability of the results to the intended treatment population[1]. We hypothesize that NB-UVB phototherapy treatment of moderate to severe psoriasis at home will be non-inferior to office treatment according to outcomes that matter to patients, providers, and payers. It is possible that home vs. office based phototherapy will be associated with differences in tolerability (i.e., burns) in those with very fair skin type (i.e., type I/II) due to increased penetration of ultraviolet rays, and may be associated with differences in effectiveness in darker skin types (type V/VI) due to decreased penetration of ultraviolet rays. Therefore, the study will be stratified by skin type to test for non-inferiority in specific patient sub groups.

1.1 Background and Relevant Literature

Psoriasis is a common chronic inflammatory disease that affects over 8 million Americans[2]. The annual U.S. cost of psoriasis amounted to approximately $112 billion in 2013[3]. The onset of psoriasis most commonly occurs in young adulthood but may start at any age ranging from the perinatal period to patients in their nineties[4]. Psoriasis affects all races and ethnicities. It is slightly more common in Caucasians compared to African Americans; however, African Americans are reported to have more severe disease[5]. Once psoriasis starts, it is a chronic, incurable, life-long disease, with durable spontaneous remissions being rare. Psoriasis is characterized by thick, inflamed, red patches (called plaques), with silver adherent scale. Plaques may be painful, itch, or burn and frequently bleed resulting in stains to clothes and bedding. Any area of the body can be affected including the face, trunk, extremities, palms, soles, genitals, and nails. Psoriasis is not "just a skin disease". It has profound impacts on health related quality of life that are similar to or more significant than other major disorders such as cancer, cardiovascular disease, and depression[6, 7]. Indeed, patients with psoriasis, particularly when disease is more extensive, have an increased risk of diabetes, chronic kidney disease, and major cardiovascular events independent of traditional risk factors, culminating in an estimated 5-year reduction in life expectancy[8-12].

The cause of psoriasis is unknown. There is genetic susceptibility with 40% of patients having a positive family history[13]. Over 80 genes predisposing to psoriasis have been identified with HLA-C gene Cw6 serotype being most commonly implicated[13]. Psoriasis is a prototypical example of a Th1/Th17 inflammatory disease characterized by increased activity of lymphocytes, antigen presenting cells, monocytes, and neutrophils resulting in dramatic increases in epidermal hyper proliferation and angiogenesis[14]. For example, in normal skin it takes 30 days for keratinocytes (the primary cell of the epidermis) to turn over, whereas this process takes only 2-3 days in a patient with psoriasis.

Treatment of psoriasis includes topical ointments, ultraviolet light phototherapy, oral medications such as methotrexate, and injectable biologics[15]. Treatment selection is based on objective factors (extensiveness of disease and anatomic areas involved) and subjective factors such as symptoms and impacts on health related quality of life. When disease is more extensive, typically affecting 3-10% (moderate) or >10% (severe) of the body surface area, topical medications are unable to control the disease and thus systemic medications or phototherapy is indicated[15]. It is estimated that about 20% of patients with

psoriasis have moderate to severe disease, culminating in over 1.5 million people in the United States[2]. Despite advances in treatments, psoriasis, particularly when moderate to severe, remains widely untreated and patients remain dissatisfied with their level of disease control[16]. For example, it is estimated that 70-90% of patients with severe psoriasis are currently not receiving systemic or phototherapy[17, 18]. Thus, the overwhelming majority of patients with moderate to severe psoriasis in the US live for decades with their disease poorly controlled[19]. Moreover, disparities exist in that African Americans are more likely to experience moderate to severe psoriasis compared to whites yet are 70% less likely to receive treatments for moderate to severe psoriasis[5, 20].

Phototherapy is a preferred first line treatment because oral medications can result in serious organ damage and/or significant gastrointestinal intolerance and biologics suppress the immune system and have warnings for infections and malignancy[21 22]. Phototherapy was first used to treat psoriasis in the 1920s and is a widely accepted standard of care[23]. In the 1980's split body studies demonstrated that NB-UVB (311 nm) was more efficacious than traditional broadband (290-320 nm) ultraviolet B (UVB) phototherapy[23]. It is important to distinguish narrowband phototherapy, which can be delivered via medical devices in the home or office, from commercial tanning beds which deliver predominantly ultraviolet A radiation and are ineffective for psoriasis. Guidelines of care issued by the American Academy of Dermatology highlight that NB-UVB phototherapy is a widely accepted, first line, standard of care treatment and also indicate that patients with psoriasis who are compliant, motivated, and adherent with instructions and follow-up examinations could, under dermatologist supervision, be considered appropriate candidates for home NB-UVB therapy[23]. Phototherapy remains a critical therapeutic modality that is much more widely prescribed by dermatologists than systemic treatments such as biologics (which are prescribed only by an estimated 20% of dermatologists)[24]. Although phototherapy does not treat psoriatic arthritis (PsA), it is often used to augment response to systemic agents and the majority of patients do not have PsA[23, 25]. Despite home phototherapy being highly preferred by patients, as summarized by a recent review of psoriasis treatment for UptoDate, "uncertainty regarding the safety of home units has led to a reluctance to prescribe them."[26] NB-UVB requires treatments three times per week for 12 weeks in order to achieve optimal skin clearance. Treatment may then continue on a maintenance basis (1-2 times per week) or be stopped and then restarted when psoriasis recurs and is symptomatic enough that the patient desires another course of phototherapy[27]. As a result, office based phototherapy is highly burdensome for patients who need to take time off from work and family to receive treatment. Moreover, only about 10% of counties in the US offer office based phototherapy[28].

1.2 Name and Description of the Comparator Product

Daavlin 7 series 3 panel narrow band phototherapy home units have 8-12 bulbs and a smaller, flat surface with a door, and measure 21" wide, 74.5" tall, and 23.5". The unit will have a dosimetry controller, a UV sensor built in that measures the intensity of the light. This unit is a class II device with an FDA 510K indication for psoriasis, vitiligo and atopic dermatitis/eczema.

1.2.1 Nonclinical Data

Not applicable

1.2.2 Clinical Data to Date

Both home and office based phototherapy are widely accepted as standard of care for patients with psoriasis as evidenced by American Academy of Dermatology treatment guidelines[23]. A recent systematic review identified nine randomized controlled trials of office-based NB-UVB phototherapy involving a total of 293 patients. The average response rate based on a 75% improvement in the Psoriasis Area and Severity Index (PASI 75) was 65% (95% CI 45-79) (PASI 75 is similar clinically to being clear/almost clear by PGA)[29]. Home phototherapy was introduced in the 1970's; however, rigorous published studies are scant. There is only one controlled trial of home narrowband phototherapy versus office-based phototherapy (no other randomized controlled studies exist)[30]. The study was conducted in the Netherlands at 14 Dermatology Departments located in hospitals with the majority of patients coming from just 4 centers. 94 patients were treated at home and 91 in the office. 41% of patients achieved a PASI75 in both groups and the authors concluded that UVB phototherapy administered at home is

equally safe and equally effective, both clinically and for quality of life, as UVB phototherapy administered in an outpatient setting[30].

1.2.3 Clinical Studies in Children

Phototherapy is generally effective and safe in children and is considered standard of care for the treatment of pediatric psoriasis;[31-34] however, prospective trials are very limited. To date, there have been 2 prospective studies of office-based UVB therapy in pediatric patients with psoriasis. Twenty children between the ages of 6 and 14 years old were enrolled in a single-center trial of twice weekly NB-UVB in a dermatology clinic in India, with 12 (60%) showing PASI 90, 3 (15%) showing PASI 70-90, 1 (5%) showing PASI 50-70, and 2 (10%) showing less than PASI 50 or worsening disease after 12 weeks[35]. The only reported adverse event was mild erythema in 2 (10%) patients. The same center also performed a prospective single-blinded trial comparing twice weekly NB-UVB versus NB-UVB with mineral oil pretreatment in a split-body design; of the 18 patients analyzed, both groups had large reductions in the mean modified PASI score (mean baseline score of 15.3 to scores of 0.64 and 0.14 at 12 weeks in the NB-UVB and NB-UVB mineral oil pretreated groups, respectively)[36].

The majority of efficacy and safety data for UVB use in pediatric psoriasis in the literature are based on retrospective reviews. In one of the largest reviews to date, 79 children with psoriasis were treated with NB-UVB at a single institution in Israel between 1998-2006; among them, 40 (51%) achieved complete clearance, 33 (41%) at least 75% improvement, and 6 (8%) less than 75% improvement. Side effects were minor and included 13 (15%) patients with mild erythema, 2 (1%) with itch, and 3 (3%) with burning[37]. In other smaller retrospective reviews, response rates have ranged from 63-88% of patients achieving clear or almost clear skin; 45-86% of patients achieving 90% improvement in PASI or BSA; 17-40% of patients achieving 70-90% improvement in PASI or BSA; 20-22% of patients achieving 50-70% improvement in PASI; and 9-15% of patients with minimal or no improvement[38-43]. There have been no published studies of home UVB phototherapy for pediatric psoriasis; however, home phototherapy is widely accepted by US dermatologists for the treatment of children with psoriasis and other light responsive disorders.

1.3 Dose Rationale

The initial dose of NB-UVB phototherapy is based on skin type. The dose is then gradually increased as tolerated based on an easy to follow algorithm (see Appendix A for examples). The initial treatment may only require 20 seconds of phototherapy exposure, which then may range to up to approximately 5-10 minutes of exposure time. The ideal dose causes mild transient pinkness of the skin that lasts < 24 hours. There are six skin types which are grouped into 3 sub-groups based on the anticipated minimal erythema dose response to phototherapy: Type I and II (white; very fair; red or blond hair; blue or green eyes; freckles, usually or always burns, never tans or tans with difficulty), Type III and IV (cream white to olive brown skin, sometimes to rarely burns, gradually tans or tans with ease), Type V and VI (dark brown, black, very rarely or never burns, tans very easily). We will therefore pre-specify three groups for analysis (type I/II, type III/IV, and type V/VI). It is possible that home vs. office based phototherapy will be associated with differences in tolerability (i.e., burns) in those with very fair skin type (i.e., type I/II) due to increased penetration of ultraviolet rays, and may be associated with differences in effectiveness in darker skin types (type V/VI) due to decreased penetration of ultraviolet rays. An example of the dosing regimen can be found in the Appendix A.

2 Study Objectives

2.1 Primary Objective

To compare the effectiveness, safety (tolerability), and duration of treatment response at 12 weeks of home versus office-based NB-ultraviolet B phototherapy for the treatment of psoriasis

2.2 Secondary Objectives

To assess the impact of phototherapy delivered at home or in the office on:

- Body surface area (BSA) affected by psoriasis multiplied by the PGA (BSAxPGA)
- Phototherapy number and dose

- Concomitant topical psoriasis treatment
- Concomitant oral or biologic psoriasis treatment
- Patient reported time spent on phototherapy
- Patient reported time and cost associated with travel
- Duration of treatment response during observation period

3 Investigational Plan

3.1 General Design

The design is a large pragmatic randomized active comparator study of home vs. office based NB-UVB phototherapy for the treatment of psoriasis. Both comparator treatments are considered standard of care and thus this would be classified as a Phase IV study. Dosing of phototherapy will be based on a standardized protocol (see APPENDIX A) or a standard protocol that is routinely used by the local investigators in order to reflect routine clinical practice. The study will include up to 1050 patients stratified by Fitzpatrick skin type (350 skin type I/II, 350 skin type III/IV, we anticipate that approximately 80 participants will be enrolled in Skin type V/VI). We hypothesize that home phototherapy will be non-inferior to office based phototherapy. There will be a recommended screening period of up to 28 days, to allow for obtaining informed consent and administrative procedures necessary for office based or home phototherapy, as well as randomization. Patients will be randomized (1:1) to home vs. office-based phototherapy within 28 days of the baseline visit or per standard of care of individual practices. If the patient is randomized to home phototherapy a machine will be delivered to their home and phototherapy treatment initiated within 14 days of randomization. If the patient is randomized to office phototherapy, the first treatment should occur within 14 days of randomization. The patient will be assessed by the dermatologist (or PA or NP or other qualified clinician as appropriate to the clinical practice) at baseline and at 12 (plus or minus 2) weeks after start of phototherapy, or at the time of discontinuation of phototherapy, whichever comes first. Patients will receive phototherapy treatments about 3 times per week for 12 weeks. They will then be observed for an additional 12 weeks. With each phototherapy treatment, patient response to prior phototherapy treatment will be collected by clinic staff or recorded on the phototherapy machine via patient assessment. Patients will complete a survey every 4 weeks for the duration of the study that captures patient reported outcomes.

3.1.1 Screening Phase

Patients will be recruited from the sites' clinical practice. Patients being considered for phototherapy will be offered the opportunity to participate in this study at the discretion of the clinician. Electronic consent will be obtained before any study specific procedures are conducted. Electronic assent will be obtained from children eligible to participate and written consent will be obtained by their parent or authorized legal guardian. Consent and assent can be obtained remotely or in person.

The screening phase begins at the time of obtaining informed consent and continues until the patient is randomized (up to a total of 28 days or longer based on the local practice standard of care). The length of time between screening and randomization will be allowed to vary based on local practice standard of care as this is a pragmatic trial and thus we aim to reflect usual clinical practice. In usual practice, clinicians vary on the duration of time between when they evaluate a patient and when the patient actually starts phototherapy. This period can be delayed due to administrative issues (i.e., obtaining insurance approvals, etc), availability of phototherapy appointments, and patient schedule issues. The baseline visit will occur during the screening phase. Information collected at the baseline visit will be collected again if the patient sees the local provider again for routine care prior to randomization. The site will confirm that the patient is eligible for randomization by having obtained any insurance approvals necessary for office based treatment and confirming with the patient that they are willing to be randomized to office based phototherapy based on any additional information obtained from the insurance approval process (such as required co-pays or other cost sharing agreement). Patients are then randomized, and should receive their first treatment within 14 days of randomization.

3.1.2 Study Intervention Phase

Patients should receive a first treatment with phototherapy according to the group they are assigned via randomization within 14 days of randomization. Patients who do not start phototherapy within 14 days of randomization will be assigned a start date at day 14 post randomization which will define their start and end of the intervention phase. Patients will be treated with home or office based phototherapy approximately 3 times per week for up to 12 weeks. The intervention stage will start on the date of the first treatment (or 14 days after randomization, whichever comes first) and continue for 84 days. Patients will be evaluated by the clinician prior to start of phototherapy (during the baseline visit) and at the conclusion of phototherapy treatment or by day 84 (plus or minus 14 days), whichever comes first.

3.1.3 Observation Phase

The observation phase will start 84 days after the first treatment is received (or 14 days after randomization, whichever comes first) by the patient and will continue for an additional 84 days.

3.1.4 Allocation to Interventional Group

Randomization will be implemented using randomly permuted blocks of size two or four, stratified on clinic and skin type. This will maximize blinding of investigators to the randomization schema and achieve balanced groups within study sites and skin types. A randomization table will be created by the senior biostatistician at the University of Pennsylvania and built into the study application ("app") by the Clinical Research Computing Unit (CRCU). The app will be loaded on iPads used to collect data by the study sites. When a new patient is enrolled in the study, the app will generate a new patient id and provide a treatment assignment. The master list of patient ids and treatment assignments will be stored electronically at the CRCU. Data analysts will be blinded as to group assignment by using codes for randomization groups.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

The first primary effectiveness outcome is treatment response, a dichotomous indicator of whether a patient has achieved clear/almost clear skin (score of 0 or 1), based on the Physician's Global Assessment (PGA) at the earlier of week 12 or discontinuation of phototherapy. See Appendix B for PGA tool.

The second co-primary outcome is the patient-reported Dermatology Life Quality Index (DLQI) at week 12. We will dichotomize DLQI at a score of 0-5 (corresponding to no to small impact on quality of life) versus a score ≥6[44].

3.2.2 Secondary Study Endpoints

- DLQI score of ≤1 (no impact on HrQOL)
- Achievement of a Minimal Clinically Important Difference (MCID) on the DLQI
- Concomitant topical psoriasis treatment
- Concomitant oral and biologic psoriasis treatment
- Patient reported time spent on phototherapy
- Patient reported time and cost associated with travel for phototherapy treatments
- Change in the product of BSA times PGA relative to baseline (BSAxPGA). See Appendix B for BSA tool.
- Duration of treatment response during observation period
- Phototherapy number and dose

3.2.3 Primary Safety Endpoints

The primary safety outcome is the proportion of patients reporting treatment-emergent adverse events. Adverse events include patient reported burns and their severity. Patients will be queried about these events immediately prior to each phototherapy treatment by the clinical staff (for patients assigned to office base phototherapy) or by the home phototherapy machine. We will also evaluate all serious adverse events regardless of their relationship to treatment. All patients will be queried about SAEs by the sites at the visit 2. Patients can spontaneously report SAEs at any point during the study.

4 Study Population and Duration of Participation

4.1 Inclusion Criteria

Inclusion criteria:

1. Willing and able to provide informed consent (age 18+) or parental permission and assent (ages 12-17)
2. Age 12 or older
3. Plaque or guttate psoriasis predominantly located on trunk and/or extremities, with a physician global assessment average of >1.0, and considered a candidate for phototherapy
4. Patient is deemed willing and able to comply with either in-office or in-home phototherapy:
    a. In office: Able to travel about 3 times per week for 12 weeks from home, work and/or school during business hours of local site
    b. In home: Has space to accommodate home phototherapy unit and patient (or if 12-17, parent), willing and able to follow home phototherapy instructions
5. New or established patient in the practice

4.2 Exclusion Criteria

Exclusion criteria:

1. Patients who are judged unable or unwilling to comply with either in office or in home phototherapy due to time, work, school, or other financial constraints
2. Patients judged unable to follow home phototherapy protocol due to failure to demonstrate understanding of the following:
    a. How to operate the phototherapy device
    b. How to follow the dosing protocol
    c. Requirement to wear protective eyewear and genital protection equipment
3. Patients with known history of lack of efficacy to phototherapy or treated with phototherapy 14 days prior to baseline visit.
4. Psoriasis predominantly located on scalp, body folds, genitals, palms and/or soles or with a physician global assessment average of ≤ 1.0
5. Patients deemed unsafe to be treated with phototherapy:
    a. History of photosensitivity or autoimmune disease such as lupus or dermatomyositis which can be aggravated by ultraviolet radiation
    b. History of arsenic intake
    c. Unable to tolerate standing for required duration of treatment due to age or physical function
    d. History of melanoma or multiple non-melanoma skin cancers that in the opinion of the principal investigator contraindicates treatment with phototherapy
6. Clinical site deems the participant is ineligible for reason other than eligibility or screening criteria.

4.3 Subject Recruitment

Patients will be recruited from approximately 20-40 sites across the United States by dermatologists who offer office-based phototherapy. The patients will be recruited during routine clinical evaluation when the patient and physician (or appropriate provider such as physician assistant or nurse practitioner) are embarking on a course of treatment for plaque or guttate psoriasis.

4.4 Duration of Study Participation

The screening period is up to 28 days or longer based on the local practice standard of care. The total duration of participation after starting phototherapy is 168 days (i.e., intervention and observation periods). The total participation including the screening period is up to 196 days but could be longer as the screening period length will be determined by local standard of care.

4.5 Total Number of Subjects and Sites

Recruitment will end when 1050 subject are randomized.

4.6 Vulnerable Populations

While the study will not specifically target pregnant women, any pregnant women who meet eligibility criteria would be able to enroll as phototherapy is a standard of care psoriasis treatment during pregnancy. Children that meet the eligibility requirements will be able to enroll. Assent from the child and written consent from the parent or authorized legal guardian will be obtained in accordance with the provisions of Subpart D, 45 CRF 46. Prisoners, fetuses or neonates will not be included in the study.

5 Study Intervention

5.1 Description

The comparator devices are the Daavlin 7 series 3 panel narrow band phototherapy home units (with 8-12 bulbs and a smaller, flat surface with door, measuring 21” wide, 74.5” tall, and 23.5”). This unit is a class II device with a FDA 510K indication for psoriasis, vitiligo and atopic dermatitis/eczema. The unit will have a dosimetery controller, a UV sensor built in that measures the intensity of the light. This sensor will adjust the treatment time to compensate for any variation in output due to aging of the lamps or other factors.

The reference device is office based narrow band phototherapy (units typically have at least 24 bulbs in a surround structure).

5.2 Intervention Regimen

Starting dose will be based on Fitzpatrick skin type (as ascertained by the clinical practice) and will increase based on the patient’s response to the treatment. The clinicians will be allowed flexibility in deviating from this regimen based on their local practice. See Appendix A for example standardized protocol.

5.3 Receipt

The home phototherapy device will, upon order from the investigators, be shipped by common carrier in a returnable packing box to the patient specified by the investigators. The unit is a single phototherapy unit that will require unpacking and minimal assembly upon receipt. Upon notification of receipt, technical assistance staff at the device supplier will contact the patient to ensure that the device was received in good order and to answer any operational questions the patient may have as is standard practice.

5.4 Storage

The home phototherapy device should be used in a private area of the home and must be near electrical service and in a place free from temperature and environmental extremes. There are no sterilization requirements for the device. The patient must wear protective eyewear during the treatment and ensure that other family members or pets are not exposed to incidental ultraviolet radiation from the device.

5.5 Preparation and Packaging

The home phototherapy device will be shipped to the patient in a re-usable shipping container that measures approximately 80” x 23” x 16”. It will be packed at the manufacturer’s facility in Bryan, Ohio.

The investigational plan is for provision of just one type of phototherapy device for all patients so there are no requirements for size selection, configuration, etc, which is typical of standard practice.

5.6 Administration and Accountability

The study site will provide a prescription to Daavlin for patients randomized to home phototherapy. See Appendix C for prescription template. Participants randomized to home phototherapy will receive instructions, as approved by Daavlin and the study investigators, on how to properly use the investigational devices at home. The device will be equipped with software programmed to provide treatments as prescribed by the physician. The software also will restrict the number of treatments a participant can receive based on a unique PIN system. At the conclusion of the LITE Study or upon a participant's withdrawal from the LITE Study, whichever first occurs, at the direction of the PI, Daavlin will provide home participants with a prepaid shipping label and shipping instructions for the return of the device to Daavlin. The PI and Daavlin acknowledge that not all devices provided for use in the LITE Study will be returned to Daavlin.

5.7 Subject Compliance Monitoring

Compliance will be measured by evaluating the number of study treatments received. Patients receiving home phototherapy will have this recorded by the home phototherapy device. Home phototherapy treatments will be verified via software obtained from the device upon their return to Daavlin. The data obtained from the devices will be considered the primary data for analysis. Patients randomized to office based phototherapy will have their treatments entered by the site staff. It is expected that patients will receive up to 36 treatments. Patients who receive at least 29 treatments will be viewed as compliant for the purposes of sensitivity analyses.

5.7.1 Return or Destruction of Investigational Product

The investigational device will be returned to the manufacturer upon the patient's completion of their treatment regimen and at the direction of the investigators. The device manufacturer will call the patient to provide instruction and answer any questions as to how to re-pack the device, affix the shipping label and prepare it for transportation back to the manufacturer.

6 Study Procedures (Appendix D)

6.1 Screening Period /Baseline Visit (recommended Day -28 to -14)

- Informed Consent/Assent
- Clinician measured PGA score
- Clinician measured BSA assessment
- Review Inclusion/Exclusion Criteria
- Demographics & Medical History
- Prior psoriasis medications and therapies
- Concomitant medications
- Patient reported DLQI
- Patient reported time spent on travel, cost of travel, (administered by the site)
- Patient reported target lesion image (staff assist for first image)
- Verify Insurance and record co-payment
- Inform participant of copayments
- Confirm patient's willingness to be randomized

Interim/ Set Up -14 to -1

- Randomize
- Prescribe and dispense home phototherapy machine for patients randomized to home treatment
- Schedule first phototherapy sessions, for patients randomized to office treatment

6.2 Study Intervention Phase Weeks 1-12

6.2.1 Week 1

- Administer NB-UVB phototherapy three times per week
- Patient reported DLQI (complete prior to first phototherapy treatment)
- Patient reported target lesion image taken prior to first treatment
- Patient reported psoriasis topical treatment
- Patient reported response to phototherapy prior to treatments. For those on office treatment, data is entered by the sites. For those on home treatment, data is recorded on the home device.
- Phototherapy session number and dose. For those on office treatment, data is entered by the sites. For those on home treatment, data is recorded on the home device

6.2.2 Weeks 2,3,5,6,7,9,10,11

- Administer NB-UVB phototherapy three times per week
- Patient reported response to phototherapy prior to treatments. For those on office treatment, data is entered by the sites. For those on home treatment, data is recorded on the home device.
- Phototherapy session number and dose. For those on office treatment, data is entered by the sites. For those on home treatment, data is recorded on the home device.

6.2.3 Weeks 4 & 8

- Administer NB-UVB phototherapy three times per week
- Patient reported response to phototherapy prior to treatments. For those on office treatment, data is entered by the sites. For those on home treatment, data is recorded on the home device.
- Phototherapy session number and dose. For those on office treatment, data is entered by the sites. For those on home treatment, data is recorded on the home device.
- Patient reported DLQI
- Patient reported target lesion image
- Patient reported psoriasis topical treatment

6.2.4 Week 12

- Administer NB-UVB phototherapy three times per week
- Patient reported response to phototherapy prior to treatments. For those on office treatment, data is entered by the sites. For those on home treatment, data is recorded on the home device.
- Phototherapy session number and dose. For those on office treatment, data is entered by the sites. For those on home treatment, data is recorded on the home device.
- Site reported concomitant oral and biologic psoriasis medications

6.2.5 End of Treatment/ Visit 2 (occurs at Week 12 (plus or minus 2 weeks) or at time that patient discontinues phototherapy, whichever comes first)

- Clinician measured PGA score
- Clinician measured BSA assessment
- Patient reported DLQI
- Patient reported time spent on travel, cost of travel, and time spent on phototherapy (administered by site)
- Patient reported target lesion image
- Site reported concomitant oral and biologic psoriasis medications
- SAE Assessment

6.3 Observational Period (Weeks 13-24)

6.3.1 Week 16, 20 & 24

- Patient reported DLQI
- Patient reported target lesion image
- Patient reported psoriasis topical treatment
- Site reported oral and biologic psoriasis medications (at week 24)

6.4 Unscheduled Visits

- Record reason on the Unscheduled Visit CRF

6.5 Subject Withdrawal

As this is a real-world pragmatic study, patients should be encouraged to continue in the study regardless of their response or adherence to phototherapy. Participants may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the site investigator for lack of adherence to study procedures, or visit schedules, or for safety or administrative concerns. Reasons for withdrawing a subject from the study will be documented by the investigator. Patients withdrawn after randomization will not be eligible for rescreening. Patients withdrawn prior to randomization may be rescreened with the approval of the PI (Dr. Gelfand). Subjects withdrawn for loss to follow up should have been called by phone at least 3 times and have a certified letter sent to the subject requesting information necessary to complete the withdrawal process. If the subject does not contact the site within 30 days of sending of the certified letter, they will be defined as lost to follow up.

6.5.1 Data Collection and Follow-up for Withdrawn or Early Termination Participants

Participants who withdraw consent to participate in the study will be asked to report the reason for withdrawal.

7 Study Evaluations and Measurements

The data collected in this study are all considered relevant for routine clinical care. In routine clinical care, there is some variation in which assessments are conducted and thus we will standardize assessments for the purpose of the study.

<u>Investigator reported measures:</u>

1. Physicians Global assessment (PGA): This is a three item measure that asks the physician or his or her designee to assess the thickness, redness, and scale of psoriasis plaques.
2. Body Surface Area (BSA): This is a measure that asks the physician or his or her designee to assess the body surface area affected by psoriasis using the handprint method in which the palm of the entire hand approximates 1% of the body surface area. To do this, the patient's handprint, including the entire area of the palm and all 5 digits with the fingers close together but not overlapping, is used as a guide to estimate 1% of the BSA
3. Number of phototherapy treatments and dose received: This data is routinely collected in clinical practice. It will be reported by the sites for patients receiving office treatment and will be obtained from the machines for those receiving home based treatment
4. Copay for office-based phototherapy
5. Concomitant treatment

<u>Patient reported measures:</u>

1. Dermatology Life Quality Index: (DLQI): DLQI is a 10 item survey that asks patients questions about their health related quality of life on a 0-3 scale. DLQI is routinely used in clinical trials of psoriasis treatments and can also be used routinely in clinical practice.

2. Patient reported response to phototherapy: This is a standard question asked to the patient to document the degree and duration of erythema induced by the prior phototherapy treatment session. It is standard of care.
3. Patient reported time spent on travel, cost of travel, and time spent on phototherapy
4. Patient reported concomitant psoriasis topical treatment
5. Photograph of target psoriasis lesion (at a subset of study sites)

7.1 Medical Record Review

Most data collected for the LITE study should be present in the medical record (source document) as part of routine documentation. Some data may be abstracted from the medical record or documented as part of completing the electronic case report forms (CRF) for the study. Below are examples of some variables which may already be present in the medical record.

- Demographics (year, date of birth, sex, marital status, education, employment status, annual household income, insurance type, race, ethnicity)
- Height
- Weight
- PGA, BSA
- Prior and concomitant psoriasis treatment
- Psoriasis date of onset
- Psoriatic arthritis presence and date of onset if present
- Major medical comorbidity
- Family history of psoriasis
- Fitzpatrick skin type (description of skin and eye color and skin's reaction to sunlight)
- Psoriasis response to sunlight
- Smoking history
- Alcohol history

7.2 Physical Examination

A complete examination of the skin will be conducted at visit 1 and 2 as well as at any unscheduled visits if deemed necessary by the patient's clinician. A physician global assessment and body surface area affected by psoriasis will be reported from the physical examination.

7.3 Vital Signs

Vital signs may or may not be taken as part of routine evaluation but will not be collected by the study.

7.4 Other Evaluations, Measures

All evaluations are described above and included on the schedule of events, see Appendix D.

7.5 Effectiveness Evaluations

Measurements of effectiveness include PGA, BSA, and the DLQI.

7.6 Safety Evaluations

Safety will be monitored by the local clinicians.

Patients will be queried about the reaction to phototherapy (i.e., burns) immediately prior to each phototherapy treatment as is standard practice. Patients will contact the study clinicians for any significant reaction to phototherapy (a burn which requires medical attention such as one associated with significant pain that interrupts usual activities or skin blistering). Patients will be queried about SAE's at visit 2. Patients can spontaneously report SAEs at any point during the study.

8 Statistical Plan

8.1 Primary Endpoint

Primary analyses will be based on the intent to treat (ITT) population defined as all patients meeting eligibility requirements who are randomized to one of the two study arms. In the ITT population, we will compare the two treatment arms with respect to two primary effectiveness outcomes. The first primary effectiveness outcome is treatment response, a dichotomous indicator of whether a patient has achieved clear/almost clear skin (score of 0 or 1), based on the Physician's Global Assessment (PGA) at the earlier of week 12 (visit 2), defined as the twelfth week after the start of treatment, or the time of discontinuation of phototherapy. In our primary analyses, patients who drop out of the study prior to achieving clear/almost clear skin or week 12, whichever comes first, will be classified as treatment failures (i.e., failure to achieve clear/almost clear skin). The second primary outcome is the patient-reported Dermatology Life Quality Index (DLQI) assessed at week 12. We will dichotomize DLQI at a score of 0-5 (corresponding to no to small impact on quality of life) versus a score >5. Patients failing to complete the week 12 DLQI assessment will be assumed to have DLQI >5 and therefore classified as a non-responder on this measure.

We hypothesize that effectiveness of home-based UVB phototherapy will not be inferior to that of office-based phototherapy on either of the two primary effectiveness outcomes. At the conclusion of the trial we will report the response rate, i.e. the proportion of patients achieving clear/almost clear skin on the PGA at the earlier of 12 weeks after initiating home or office-based phototherapy or discontinuation of phototherapy and the proportion of patients with no to small impairment on quality of life (DLQI 0-5) at week 12 for each treatment arm with 95% confidence intervals. These measures will be reported for the complete study cohort and separately for two of the three skin type sub-groups. We will not be able to test the hypothesis of non-inferiority of home vs. office treatment in skin type V/VI. We will accumulate additional data in this group which will improve the precision of our estimates of efficacy in this patient population as well as gather additional data about barriers patients with skin type 5/6 face in accessing home or office base phototherapy that lead to inequities and health disparities in patients with psoriasis.
To account for stratification by skin type, which induces non-independence across strata, pooled analyses will be conducted using logistic regression adjusted for treatment arm and skin type. Skin-type adjusted risk differences between home and office-based phototherapy will be computed from odds ratios using marginal standardization. Statistical inference will be based on adjusted risk differences according to non-inferiority principles. Home-based phototherapy will be determined to be non-inferior relative to office based phototherapy if the lower bound of the adjusted two-sided 95% confidence interval for the risk difference is greater than the pre-specified non-inferiority margin of 15%.

8.2 Secondary Endpoints

In addition to pooled analyses described above, separate analyses will be conducted for each skin type using a non-inferiority margin of 15%. The estimated risk difference in dichotomized DLQI at week 12 and PGA at or before week 12 will be estimated empirically based on the proportion of patients achieving the endpoint in each skin type sub-group and study arm. We will also assess heterogeneity of treatment effect (HTE) across the three skin types using logistic regression. In this analysis, we will fit models for each of the two primary outcomes with skin type, treatment arm, and their interaction as predictors. HTE will be assessed using an omnibus Wald test of all interaction regression parameters for each outcome of interest in order to minimize multiple testing and consequent alpha inflation.

In secondary analyses, we will investigate additional outcomes:

- Total number of phototherapy treatments received
- Cumulative dose of phototherapy
- Frequency of topical concomitant psoriasis treatment
- Changes in initiation, dosing, or discontinuation of oral or biologic psoriasis treatments
- Patient-reported amount of time spent on phototherapy
- Patient reported travel (cost and time)
- DLQI score of ≤1at week 12

- MCID on DLQI at week 12[45]
- Physician reported change in the product of body surface area (BSA) times PGA (both as a continuous measure and as a dichotomous measure evaluating a 75% and 90% reduction in the BSAxPGA).
- Duration of treatment response
- Percentage of patients receiving ≥ 80% of assigned treatments

Because we have no a priori hypothesis of equivalence between treatment arms on these outcomes, these analyses will be conducted using standard hypothesis testing principles. We will report the mean (for continuous measures) or frequency (for binary measures) and 95% CIs for each measure within treatment arms as well as the difference in means or frequencies between treatment arms and the 95% CI of the difference. Secondary outcomes will be measured with a frequency as described in Appendix D, Schedule of Study Procedures. We will analyze these measures using linear or logistic regression models with robust variance estimators via Generalized Estimating Equations (GEE) to account for within-patient correlation that occurs with repeated measures. Regression models will include terms for treatment arm, time since randomization (categorical), skin type, and the treatment arm/time interaction. Inclusion of the interaction term will allow us to assess possible variation in effectiveness of home phototherapy relative to office-based phototherapy over time. Physician reported outcomes (PGA times BSA) will be measured at baseline and at the earlier of week 12 or upon discontinuation of phototherapy, whichever comes first. We will compare this outcome between home and office-based phototherapy arms using linear regression adjusted for skin-type. All secondary analyses will be repeated within each skin type stratum.

During the follow-up observation period, weeks 13-24 after start of therapy, we will compare dichotomized DLQI, and receipt of concomitant topical psoriasis treatment between study arms. These measures will be assessed every four weeks during the observation period and analyses will use the same approach as described above for other secondary outcomes. We will also assess change in oral or biologic psoriasis treatment during the observation period at week 24.

Duration of response will be measured in patients who achieved a DLQI score of 5 or less at week 12, are no longer receiving phototherapy, and who have not initiated a new systemic treatment or had dose escalation of an existing psoriasis systemic treatment at any point during the study. Duration of response will be defined as the length of time from week 12 to the earliest of DLQI > 5 or time of initiation of a new systemic treatment or dose escalation of an existing systemic treatment, with patients who maintain DLQI $\leq$ 5 throughout the 12 week observation period with no new systemic treatments or dose escalation censored at week 24. In order to obtain results that are generalizable to the full ITT study population, we will use inverse probability weighting to account for possible selection bias due to differences between characteristics of participants included in this analysis and the full study population. Duration of response will be analyzed using a Cox proportional hazards regression model adjusted for treatment arm, skin type, and their interaction. Based on results for the interaction term between study arm and skin type, we will report differences in duration of treatment response between study arms by skin type.

8.3 Sample Size and Power Determination

Our study has been powered to allow us to determine non-inferiority of effectiveness both overall and within two of the three skin type strata. Because a clinical question is whether effectiveness is equivalent within each skin type sub-group, our sample size has been determined in order to provide adequate power for these skin type-specific analyses. We have pre-specified two primary effectiveness outcomes and assume a type I error rate for each outcome at the one-sided alpha = 2.5% level which is standard for a non-inferiority trial and analogous to the more familiar two-sided alpha = 0.05. Although this alpha level does not explicitly account for multiple comparisons, we believe that doing so would be unnecessarily conservative as both our patient-reported and physician-reported outcome measures assess the same outcome and are expected to be very highly correlated[46]. Assuming a 50% response rate in both the office based phototherapy group and the home-based group and a non-inferiority margin of 15% (i.e. the 95% two-sided confidence interval on the difference in response rates between office and home-based groups excludes 15%), we calculated that 175 patients of each skin type would need to be included in each study arm to have 80% power to establish non-inferiority of home based phototherapy at a one-sided significance level of 2.5%. In the pooled sample, we will have 99% power for a non-inferiority

margin of 15%. Our non-inferiority margin has been iterated with our patient research partners and expert dermatologists. It is well within previous suggestions of non-inferiority for psoriasis treatments[47]. We also note that the FDA accepts a 15% margin or greater for the study of biosimilars of biologics for moderate to severe psoriasis[48, 49]. Additionally, our estimates are more conservative (i.e., require a larger sample size) than the non-inferiority margin specified in the pragmatic trial of home versus office based phototherapy conducted in the Netherlands which only required 100 patients per group total[30]. Our estimates require a larger sample size compared to the Netherlands study primarily because we have set a higher bar for effectiveness. Based on preliminary data, the rate of DLQI ≤5 is anticipated to be similar to the estimate of achieving clear or almost clear skin, providing 80% power for the same non-inferiority margin for this outcome[15].

8.4 Statistical Methods

8.4.1 Baseline Data

Our initial analyses will utilize descriptive statistics to detail the characteristics of the study cohort. Continuous variables will be described with means and standard deviations. Categorical variables will be summarized using counts and proportions. Summary statistics will be generated for the full study cohort as well as stratified by treatment arm, skin type, and the combination of treatment arm and skin type. Imbalance in covariates between the home and office based phototherapy arms will be described by calculating the differences in means or proportions between the two arms with 95% confidence intervals.

8.4.2 Efficacy Analysis

The primary efficacy endpoint is both physician reported (the physician global assessment) and patient reported (DLQI) The efficacy analysis approach is detailed in section 8.1 and 8.2.

8.4.3 Safety Analysis

The primary safety outcome is the proportion of patients reporting treatment-emergent adverse events. Adverse events include patient reported burns and their severity. We hypothesize that safety of home based UVB phototherapy will not be different from office based phototherapy. We anticipate based on extensive experience, that the number of clinically significant burns (i.e., which may require the patient to seek advice from the treating physician and occur due to human error) will be rare (affecting <1% of patients) and typically can be managed at home with over the counter remedies.

As ultraviolet light does not have adverse effects beyond the skin, our stakeholders believe that safety assessments should focus on skin related events such as burns and serious adverse events. We will summarize the number, severity, and type of adverse events experienced by patients in each treatment arm. We will compute the proportion of patients experiencing adverse events by treatment arm, with 95% CI. Similar to analyses for our effectiveness outcomes, we will also fit skin type-adjusted logistic regression models and use standardization to estimate adjusted risk differences between treatment arms. In addition to pooled safety analyses, we will also compare the proportion of patients experiencing adverse events between office-based and home-based phototherapy arms within each skin type sub-group

8.4.4 Exploratory Analysis

In addition to the primary ITT analyses described above, we will conduct an “as treated” analysis in order to evaluate those who completed the study and received at least 80% of treatments. We will evaluate the effects of indirect costs (i.e., co-pays), treatment center, season, geography, and psoriasis characteristics (such as plaque thickness) on response rate. Additional exploratory analysis will be conducted by request of our stakeholder committees upon review of the data (these will be designated post hoc). Exploratory and post hoc analyses will be interpreted with caution and taking into consideration the total number of post hoc comparisons that have been conducted.

8.4.5 Missing Data Strategy

Our analysis strategy for the primary outcome of clear/almost clear skin and the patient reported DLQI (no impact on quality of life) uses an ITT strategy by treating all patients who discontinue treatment prior to achieving clear/almost clear skin as treatment failures. Thus, for these outcomes there will be no missing data. For secondary and exploratory analyses of longitudinal outcome measures that require data from follow-up assessments, such as dosing of phototherapy, frequency of concomitant psoriasis treatment, and amount of time spent on treatment, our analysis strategy incorporates all available baseline and longitudinal information. The GEE estimator is only unbiased if data are missing completely at random (MCAR). If the total proportion of observations with missing data in a given analysis exceeds 10%, we will address loss of efficiency due to missing data and possible bias arising from violation of the assumption of MCAR missingness by undertaking multiple imputation (MI) implemented using multiple imputation via chained equations (MICE). Using MICE, we will create 10 imputed versions of the complete data set with all missing outcomes and patient characteristics imputed simultaneously. For each analysis that makes use of data elements with missingness, we will then conduct the analysis in each imputed data set and combine the results using standard rules.

We will conduct additional sensitivity analyses to explore the sensitivity of our results to possible missing not at random missingness. We will use the “tipping-point” approach to identify combinations of values for missing measures that would change the conclusion of our study and will summarize the results using graphical displays.

8.5 Subject Population(s) for Analysis

The primary analysis will be based on all subjects randomized into the study, regardless of whether they received the assigned treatment. We will also conduct an “as treated” analysis in order to evaluate those who completed the study and received at least 80% of treatments

9 Safety and Adverse Events

Designated site personnel at each site have the front-line responsibility of reviewing patient-reported response to phototherapy, identifying and documenting treatment emergent adverse events, and adjusting phototherapy dosing accordingly. The Sponsor/Study Principal Investigator is responsible for tracking these reports and relaying them, if required, to the IRBs and other investigators. For this pragmatic study, where intervention is standard of care and performed by the patient’s clinician or the patient themselves (in the case of home treatment), AE’s not related to phototherapy are not required to be recorded or followed by patient’s clinician and will not be recorded for study purposes.

9.1 Definitions

9.1.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. For the purpose of this pragmatic trial, for which the intervention occurs during standard of care visits, we will only record and collect data on adverse events that are specifically related to phototherapy treatment, except for serious adverse events which will be collected regardless of relationship to phototherapy.

9.1.2 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay

- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

9.2 Recording of Adverse Events

This pragmatic trial will be evaluating the effectiveness of two standard of care treatments, home and office-based phototherapy. All treatments will be administered and monitored by the patient's clinical care provider (dermatologist) and designated staff (typically phototherapy nurses). Recording of reported adverse events will be completed by the patient's clinical care provider(s) prior to the administration of each treatment (3 times per week) and the clinical course of each event will be followed until resolution, stabilization, or until it is determined that phototherapy is not the cause. Adverse events will be documented in the patient's medical record by the clinical care provider(s) throughout the 12 week intervention period and the subsequent 12 week observation period per local practice or medical center requirements. Only phototherapy-emergent adverse events will be abstracted from medical records and/or home phototherapy equipment and recorded for study objective purposes.

Serious adverse events will be recorded and monitored by the patient's clinical care provider(s), per standard of care practices, and will also be recorded, tracked, and reported by the study in the appropriate case report form and SAE reporting form at Visit 2. Serious adverse events that are identified at the end of the study intervention period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study intervention period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

9.3 Relationship of AE to Study

For the purpose of this pragmatic trial, for which the intervention occurs during standard of care visits, we will only record and collect data on adverse events that are specifically related to phototherapy. The Site Investigator or designee will review all AEs.

9.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

Local site investigators and the study principal investigator must conform to the serious adverse event reporting timelines, formats and requirements of the various entities to which they are responsible. If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

9.4.1 Follow-up report

SAEs that are ongoing at the time of initial report will be followed until resolution by local site investigators and will require a follow up report documenting final outcome. If new information arises that changes the

investigator's assessment of a SAE, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the various entities to which they are responsible.

9.4.2 Investigator reporting: notifying the study sponsor

Any study-related unanticipated problem posing risk to subjects or others, and any type of serious adverse event, will be reported to the study sponsor by telephone within 24 hours of the event. Report serious adverse events by phone and email to:

Joel M. Gelfand MD, MSCE
Phone: 215-662-SKIN
Email: Joel.Gelfand@uphs.upenn.edu

Within the following 48 hours, the local site investigator will document and provide further information, if available, on the serious adverse event or the unanticipated problem in the form of a written narrative report. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor. The local site investigator will keep a copy of the SAE report on file at the study site.

9.4.3 Investigator Reporting: Notifying the Penn IRB

As adverse events will be reported, recorded, and followed per standard of care practices for patients receiving office-based and home phototherapy, study sites will not be required to report AEs to Penn. Any SAE or study-related unanticipated problem posing risk to the subject or others, will be reported to the Penn IRB, per Penn IRB requirement and timelines (*http://www.upenn.edu/IRB/mission-institutional-review-board-irb/reportable-events),* as a written report of the event, including description per Section 12.4.2 above and need for revision to consent form or other study documentation). Copies of each report and documentation of IRB notification will be kept in the principal investigator's regulator binder.

9.4.4 Sponsor reporting: Notifying participating investigators

Investigators, who are not Penn faculty and not relying on Penn IRB for regulatory review, are responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements, Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file.

9.5 Medical Monitoring

It is the responsibility of the Site Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. The local clinical team (such as phototherapist, medical assistants, etc.) will monitor patient safety as is routine in clinical practice.

9.5.1 Data and Safety Monitoring Plan

The Data and Safety Monitoring Plan will be maintained by the study principal investigator (Dr. Gelfand). The DSMP describes approaches to ensuring complete and accurate data through ongoing monitoring of site data and additional monitoring as needed for sites not achieving pre-specified data quality metrics (Appendix F).

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why

- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Data Collection and Management

Patients will complete an electronic consent and HIPAA form and data will be collected via an app developed using Medable software. The app will reside on a tablet device at each site (for site entered data) and on the patient's smart phone (a smart phone will be provided for the purposes of the study to patients who do not have one). Data will be encrypted and housed on a cloud-based server operated by Google Cloud Platform and is compliant with 21 CFR Part 11, HIPAA and international privacy regulations and laws. Personally identifiable information (PII) and protected health information (PHI) will be housed in the app's account record which is separate from the study database (task and step responses from electronic case report forms (eCRFs)). Access to data collected via the app is only granted to the researchers who create the App and if other researchers would like to access the data, only the aforementioned App creators may grant this through user authentication. Authentication is available through session-based, signature-based, and single-factor authentication. Access to data, once authenticated, is managed via fine-grained access control lists. The research team may securely download and transfer data from Medable. PII and PHI will not be available to access with standard tools of data exports. PII and PHI will only be accessible to research team members with administrator roles and assignments of scripts to pull the select PII and/or PHI as needed.

All participants will receive a random identification number that will be used to identify participants' data. No direct identifiers will be used.

10.2.1 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.2.2 Case Report Forms (CRFs)

The study electronic case report form (eCRF) on the Medable app is the primary data collection instrument for the study. All data requested on the eCRFs must be recorded. All missing data must be explained. If a space on the eCRF is left blank because the procedure was not done or the question was not asked, validation rules will trigger a flag and require entry to cite reason. If the item is not applicable to the individual case, the item will not be viewable to on the eCRF for that participant.

10.3 Records Retention

As required by the agreement with PCORI, it is the investigator's responsibility to retain study essential documents for 3 years after the final study results are presented in a public forum.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

The study will be monitored according to the Data and Safety Monitoring Plan (Appendix F).

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the funding source, PCORI, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

12.1 Risks

This is a standard of care study. The main risk to study participation is to patient privacy. This risk will be mitigated by collecting minimum data necessary in order to avoid the risk of personally identifiable information becoming compromised. All data will be stored using encrypted and secured password protected systems.

12.2 Benefits

Direct benefits to study participation include modest compensation for completing study questionnaires and a 50% chance of receiving home phototherapy for 12 weeks at no cost. Indirect benefits are to society in the future as the results of this study may shift clinical practice to be more patient centered.

12.3 Risk Benefit Assessment

The balance between the risks and benefits is strongly in favor of benefit as the risks are minimal and no greater than might be encountered in daily life. All patients will receive some degree of benefit through modest compensation and 50% will benefit by having home phototherapy machines provided at no cost.

12.4 Informed Consent Process / HIPAA Authorization

All participants, or legally authorized representatives, must sign an electronic informed consent form for participation in this study prior to screening or performing any screening procedures. Participants will be informed that their participation in this study is voluntary and does not affect their usual clinical care. Subjects will be given appropriate time after the informed consent discussion to decide on their participation in the study. Study staff will obtain consent at Visit 1 in a private and quiet space via an electronic device that subjects will electronically sign. Consent and assent obtained remotely will be done through REDCap. A signed copy of the eICF and HIPAA document will be provided to the subject. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the informed consent document or a separate assent form. In determining whether participants are capable of assenting, the investigator shall take into account the age, maturity, and psychological state of the subject

involved. A parent or authorized legal guardian must sign an electronic informed consent form. Electronic assent and informed consent will be obtained in accordance with the provisions of Subpart D, 45 CRF 46. The process of obtaining informed consent should be documented by study staff on the appropriate study CRF.

Electronic informed consent and HIPAA and assent forms will be collected via an app developed using Medable software The app will reside on a tablet device at each site. The signed consents will be encrypted and housed on a cloud-based server operated by Google Cloud Platform and is compliant with 21 CFR Part 11, HIPAA and international privacy regulations and laws. Consents obtained remotely will be done through RECap. A secure linkto the appropriate consents/HIPAA documents will be emailed to the participant. Study staff will set up a time to review the ICF/HIPAA remotely via telephone or video call, and answer any questions the participant may have. Once the consent is signed and confirmed, the consent document will be saved as a PDF in REDCap's file repository. The patient can download a copy of their PDF after signing Access to the signed ICF and HIPAAs via fine-grained access control lists will be granted to the research staff.

13 Study Finances

13.1 Funding Source

The LITE Study is funded by a contract from the Patient Centered Outcomes Research Institute (PCORI).

13.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research. Local site investigators will follow their institutions policies on conflict of interest. If no policy is available, the local investigators will inform the study PI (Dr. Gelfand) and follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

13.3 Subject Stipends or Payments

Subjects will be asked to complete two study visits, Baseline and End of Intervention. These study visits will occur in conjunction with standard of care clinical visits that subjects would already attend. Subjects will not be reimbursed for time, travel, parking, copays, deductibles, or any other costs associated with study participation.

Subjects will be asked to complete questionnaires via a mobile app every four weeks starting from randomization and ending at the End of Observation Period for a total of eight times. For each questionnaire, subjects will be reimbursed $20 after questionnaire completion. Subjects who do not have access to a smart phone will be provided one throughout study duration at no cost.

If the subject does not complete all questionnaires, the amount received will be pro-rated to reflect the number questionnaires completed. In addition, subjects may need to complete a W-9 form which is required by the IRS when study participation will result in a subject receiving more than $600 in a calendar year. This form will be provided for subjects.

14 Publication Plan

The study PI, Dr. Gelfand, holds the primary responsibility for publication of the results of the study. Permission must be obtained from Dr. Gelfand before any study related information can be used or passed on to a third party.

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16 Appendices

16.1 Appendix A- Example protocol for office based phototherapy

16.2 Appendix B- Physician Global Assessment PGA & Body Surface Area BSA

16.3 Appendix C- Daavlin Phototherapy Prescription Template

16.4 Appendix D- Schedule of Study Procedures

16.5 Appendix E- Patient Questionnaires

- *16.5.1 Dermatology Life Quality Index DLQI*
- *16.5.3 Phototherapy Transportation Questionnaire*
- 16.5.4 *Phototherapy response*
- *16.5.5 Psoriasis Topical Treatment*

16.6 Appendix F- Data Safety Management Plan

16.7 Appendix G-Informed Consent Forms

16.8 Appendix H-Assent Form