Evaluating the effect of Solius UV light source in improving serum concentrations of 25-hydroxyvitamin D in vitamin D deficient/ insufficient adults of various skin types

ClinicalTrials.gov number: NCT04780776
Protocol Version Number: 2.0
Protocol Version Date: November 5th, 2020
Funding Mechanism: Provided by SOLIUS company

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Statistical Analysis Plan see pages 23-26

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TABLE OF CONTENTS

1 List of Abbreviations 3
2 Protocol Summary 3
3 Background/Rationale & Purpose 4
3.1 Background Information 4
3.2 Rationale and Purpose 7
4 Objectives 8
4.1 Study endpoint 8
4.1.1 Endpoint Measures 8
5 Study Design 9
6 Potential Risks and Benefits 13
6.1 Risks 13
6.2 Potential Benefits 15
6.3 Analysis of Risks in Relation to Benefits 16
7 Study Subject Selection 16
7.1 Subject Inclusion Criteria 16
7.2 Subject Exclusion Criteria 17
8 Study Intervention 17
9 Study Procedures 18
10 Assessment of Safety and Data Safety Monitoring Plan (DSMP) 20
10.1 Definitions 20
10.2 Safety Review 21
10.3 Reporting Plans 21
10.4 Stopping Rules 22
11 Data Handling and Record Keeping 22
11.1 Confidentiality 22
11.2 Source Documents 23
11.3 Case Report Forms 23
11.4 Study Records Retention 23
12 Statistical Plan 23
12.1 Study Hypotheses 24
12.2 Sample Size Determination 24
13 Ethics/Protection of Human Subjects 26
14 Literature References 26

1 List of Abbreviations

Abbreviation	Abbreviation definition
UVR	Ultraviolet Radiation
UVB	Ultraviolet B
25(OH)D	25-hydroxyvitamin D
SPS	Solius Photobiologic System
MED	Minimal Erythemal Dose

2 Protocol Summary

Title:	Evaluating the effect of Solius Photobiological System in improving serum concentrations of 25-hydroxyvitamin D in vitamin D deficient/ insufficient adults
Population:	Healthy adults ages >21 years; both sexes, approximately 100 adults for serum 25-hydroxyvitamin D screening, 80 adults with vitamin D deficiency/insufficiency for the main study, 40 adults for treatment group and 40 adults for sham controls
Intervention:	The study treatment is a weekly exposure to the Solius Photobiological System, which emits Ultraviolet B (UVB) Radiation. This will be accomplished with an established dose of UVB radiation for 16 weeks. SOLIUS delivers 0.6 Minimal Erythemal Dose (MED) to achieve non-perceivable erythema for a therapeutic dose.
Objectives:	To assess the safety and effectiveness of the Solius Photobiological System in improving serum concentrations of 25-hydroxyvitamin D [25(OH)D] in vitamin D deficient/ insufficient adults of various skin types
Design/Methodology:	We will conduct a double-blinded randomized clinical trial to compare the changes in serum 25-hydroxyvitamin D concentrations between subjects who receive (intervention group) and do not receive (placebo control group) weekly exposures to Ultraviolet B (UVB) Radiation generated by the Solius Photobiological System for 16 weeks. Both groups will be exposed to blue/purple light which is turned on when the device is activated. The intervention group that will be exposed to the Solius Photobiological System will first undergo an evaluation of each individual's sensitivity to the Solius Photobiological System using the device titration system for the first 5 weeks. The control group will undergo the same process and will only be exposed to the blue/purple light. After the 5 weeks, the subjects will be enrolled in a 16-week study where they will be exposed to an

	amount of time based on their individualized titration evaluation. The control group will be exposed for the amount of time based on their skin type similar to the intervention group. After finishing the 16-week intervention, the subjects will be asked to return to the study site once a week for 4 weeks for measurement of serum concentrations of 25-hydroxyvitamin D. The control group, will undergo the procedures as the treated group with the exception that the Solius Photobiological System will only be turned on to emit blue/purple visible radiation. We will enroll approximately 100 adult subjects will be enrolled for serum 25-hydroxyvitamin D screening. We expect to enroll 80 vitamin D-deficient or insufficient subjects in this study. They will be randomized to receive or not receive the UVB radiation intervention. Both groups will be exposed to the same blue/purple visible light so that the study subjects will not know whether they are receiving UVB radiation or not since UVB radiation is not visible to the human eye. Serum 25-hydroxyvitamin D concentrations will be measured monthly, and the concentrations will be analyzed to compare between those who receive and who do not receive the UVB radiation intervention for baseline and during the 16-week treatment period and the end of the study. We expect that the serum levels of 25(OH)D will increase by more than ten ng/ml after 16 weeks of intervention in the treatment group compared to control group. Subjects converted from vitamin D deficient/insufficient to insufficient/sufficient is considered a minimum clinical important difference (MCID). We expect at least 70% of vitamin D deficient/insufficient subjects in the treatment group to convert to insufficient/ sufficient. Also, because of seasonal variations and other confounders, we expect a maximum 30% of the subjects to convert to insufficient/sufficient in sham control group.
Total Study Duration:	12 months
Subject Participation Duration:	26 weeks including one week for screening, 5 weeks for titration, 16 weeks for treatment and 4 weeks for post-intervention follow up

3 Background/Rationale & Purpose

3.1 Background Information

Vitamin D deficiency has been a worldwide health problem for over a century, now affecting over 1 billion people on this planet[1]. Although technology is drastically advancing, we still are unable to put an end to this health emergency.

Vitamin D can be introduced in the body in two ways, 1) via diet and 2) through the sun. Few foods naturally contain vitamin D (either D_2 or D_3)[2] such as oily fish. For instance fresh wild salmon (3.5oz or

100g) has between 600-1000 IU of vitamin D_3. Canned tuna (3.6oz or 102 g) has about 230 IU of vitamin D_3.[2] Sun-dried mushrooms and egg yolks are also viable sources of vitamin D. Sun-dried shiitake mushrooms have about 1600 IU of vitamin D_2 whereas egg yolks have about 20 IU of vitamin D_2 or vitamin D_3 [2]. There are some fortified foods that also contain vitamin D; fortified milk and fortified orange juice each has about 100 IU/8 oz of vitamin D_3. Some cereals, such as Quaker Oatmeal has as much as 40 IU vitamin D/cup.[3] Margarine has about 60 IU of vitamin D/tablespoon.[3] In a study that looked at the plasma levels of 25(OH)D_3 amongst fish eaters and non-fish eaters (vegans and vegetarians), those who did not consume fish had lower levels of 25(OH)D_3 in both the summer months (20%) and winter months (38%).[4] Thus the consumption of fish in the diet is critical in maintaining vitamin D status throughout the year, especially during the winter months.

When assessing the optimal dietary intake of vitamin D, there might be some controversy as to which guideline to follow. The Institute of Medicine (IOM) issued guidelines to maintain adequate serum 25(OH)D levels above 20 ng/mL.[5] The Endocrine Society's guidelines reflect the needs to treat and prevent vitamin D deficiency and maintain a 25(OH)D status above 30 ng/mL.[6] One would have to consume a significant amount of fish and fortified food products to meet the above recommendations. Thus, it is critical that we incorporate sun exposure into our everyday lives, and/or take vitamin D supplements.

When ultraviolet B (UVB) radiation (wavelength of 290-320 nm) from the sun is absorbed into the skin, it converts 7-DHC, which is predominantly located in the stratum spinosum and stratum basale[7], to previtamin D_3, which is thermodynamically unstable. Over several hours it isomerizes into vitamin D_3.[8] The vitamin D_3 from the skin and the vitamin D_2 from food and supplements enters the circulation and are hydroxylated in the liver by a 25-hydroxylase to become 25-hydroxyvitaminD (25(OH)D), which is the major circulating form of vitamin D.[8-9] 25(OH)D is hydroxylated again in the kidneys by 1alpha-hydroxylase to become 1,25-dihydroxyvitamin D (1,25$(OH)_2$D), which is the active form of vitamin D. When calcium levels are too high, 24-hydroxylase activity increases, hydroxylating C24 and making, 24,25-Dihydroxyvitamin D (24,25$(OH)_2$D) and 1,24,25-trihydroxyvitamin D (1,24,25-$(OH)_3$D). This step begins the process of the degradation of both metabolites into inactive water-soluble metabolites that can be excreted in the bile. The ability to maintain 25(OH)D levels via sun exposure is influenced by the zenith angle of the sun.[10] The zenith angle is defined as the oblique angle between the sun's rays and the earth's surface. The time of day, season, and latitude on the earth's surface all affect the zenith angle. Above 37° latitude during the months of November through February, there is a significant decrease in the amount of UVB photons hitting the earth's surface, as much as 80%-100% depending on latitude [11]. Thus, for those living in areas at a zenith angle incompatible for producing vitamin D in the winter, they need to obtain their vitamin D via supplements and/or food containing or fortified with vitamin D.

Those living above 37° latitude during the months of November through February could also rely on artificial UVB light sources such as the Sperti lamp or UVB emitting LEDs. These lights permit the skin to convert 7-dehydrocholesterol into vitamin D allowing the body to maintain adequate vitamin D levels while avoiding exposure to the sun. In particular, these lights are resourceful to those having fat

malabsorption disorders such as Crohn's disease, cystic fibrosis, and/or gastric bypass. For these individuals who are unable to absorb vitamin D from the diet, exposure to UVB is the primary way of maintaining an adequate vitamin D status.

UVB phototherapy is a potential solution to the problem. Importantly, narrowband UVB (NB-UVB) phototherapy can be safely used. Long-term studies to date do not indicate a significantly increased risk of skin cancer in an age- and sex-matched control population who have not received UVB phototherapy.[20-24] In a 2005 literature review, a search from 1966 to June 2002 was conducted. Eleven studies involving about 3400 subjects (including those with >300 lifetime treatments) were included. Except for 1 Finnish study, all studies showed no increased skin cancer risk with UVB phototherapy.[25] In a 2012 systematic literature review examining NB-UVB and risk of skin cancer, four studies followed a total of 6,385 subjects. None of the four studies found an increased risk of skin cancer in psoriasis subjects treated with NBUVB. [26] The above studies were mostly in Caucasians with skin types I-III. In a 2011 study of 445 Koreans (skin type III-V) treated with NB-UVB, no melanoma cases were reported within the mean follow-up period of 34.4 months.[27] The investigators also concluded that there were no statistically significant differences in non-melanoma skin cancer between the NB-UVB and control groups. In the largest study on the safety of vitiligo treatment ever conducted, a 2020 retrospective cohort enrolled 60,321 subjects with vitiligo. [28] Subjects were classified into 5 groups: 0 sessions of NB-UVB; 1-49 sessions; 50-99 sessions; 100-199 sessions; and ≥200 sessions. 717 subjects had at least 500 phototherapy sessions. The risk of nonmelanoma skin cancer did not increase with increasing total sessions of NB-UVB. Further, the subjects who had at least 500 sessions of NB-UVB phototherapy had no greater risk of skin cancer than the subjects who did not undergo NB-UVB phototherapy at all.

Solius has created The Solius Photobiologic System (SPS), which is an experiential device that allows a user to receive a calibrated and calculated dose of vitamin D using wavelengths of UV light that facilitate the body's endogenous production of vitamin D and a variety of biologically controlled feedback mechanisms. The output of SPS is very similar to a NB-UVB device, but without the wavelengths that are less effective in endogenous vitamin D production. Exposure of individuals with varying skin types to these lights will enable us to observe the effect of artificial UVR exposure in creating vitamin D in individuals with varying shades of skin color. The benefit of this lamp will allow individuals who live in northern locations or individuals with malabsorption problems to create vitamin D.

Solius previously has completed two human clinical trials. The first study was a pilot feasibility study aimed to validate if the Solius Photobiological System efficiently stimulated the endogenous vitamin D process. The second study was a randomized non-inferiority study comparing the SOLIUS device to oral vitamin D supplements.

In a prospective cohort study (QR-TRP-002), six healthy adults with Fitzpatrick skin types I, II, and III were exposed to a 0.75 minimal erythemal dose (MED) of UVB radiation to approximately 75% of their body surface area once per week for 4 weeks. The individual dose was determined with Fitzpatrick skin typing, followed by exposure of the underneath of one forearm to 10 successively increasing durations of exposure to UVB. The subjects had a significant increase in mean 25(OH)D from 22.8 ± 13.9 ng/ml to 27.2 ± 12.0 ng/ml ($P<0.05$), representing a 19% increase over baseline after 4 weekly UVB exposures. No adverse events occurred.

Another study was performed on military personnel. Military personnel are at high risk for low vitamin D status which is common in individuals who regularly perform extreme physical exertion, particularly in combination with periods of psychological stress, inadequate nutrition, and sleep disruption. A total of 98 participants enrolled in the study; 10 (10.2%) either dropped out or were removed after enrollment. The final sample included 45 participants in the supplement and 43 in the phototherapy group. There were no between group differences noted based on age or gender distribution (P=0.06). There were also no between group differences observed with respect to race / ethnicity, Fitzpatrick skin type, birth location with respect to 37th parallel, prior diagnoses of vitamin D deficiency, vitamin D supplementation history, stress fractures, or family history of bone disorders, and total number of hours per week of sun exposure, with $P > 0.05$ for these groups.
The median serum 25(OH)D levels at baseline for the supplement and phototherapy were 25.0 ng/mL (IQR 21.0–32.0) and 28.0 ng/mL (IQR 22.0–35.0), respectively. By month three, the phototherapy group showed significantly higher levels of serum 25(OH)D than the supplement group (P=0.01, ŋ2=0.08) with a median level of 25.5 ng/mL (IQR 21.0–29.8) compared to a median level of 30.0 ng/mL (IQR 25.8-37.0) for the phototherapy group. By the four-month follow up the two groups again showed a slight difference in serum 25(OH)D levels with higher levels in the phototherapy group (P=0.04, ŋ2=0.05). At this timepoint the supplement group had decreased from baseline to median levels of 21.0 ng/mL (IQR 17.0-30.0) and phototherapy returned to baseline (median 27.0 ng/mL, IQR 22.0-32.5) (see supplementary documents).

With suboptimal intake of key nutrients like calcium and vitamin D, historically low compliance with taking pills, and low sun exposure, limited potential to optimize serum 25(OH)D continues to pose a threat to physical and mental health, disease prevention, and resilience so critical to individual wellness and readiness. At a time when self-care measures are highly valued for health promotion, programmed UVB photobiologic therapy, available as a kiosk in the community, appears to be a safe, efficacious alternative to oral vitamin D supplementation.

As discussed above, there is an ever growing need to improve the vitamin D status of the global population. Many individuals who live above 37° latitude and/or have malabsorption problems will greatly benefit from an artificial light source to combat their increased risk for vitamin D deficiency. The purpose of this study is to observe the effects of exposure of individuals of varying shades of skin color to Solius light source. The findings from the study have enormous health implications as it could be a potential treatment plan for many people battling vitamin D deficiency.[8,11,13]

This study will be conducted in compliance with the protocol, applicable regulatory requirements, and BMC/BU Medical Campus Human Research Protection policies and procedures.

3.2 Rationale and Purpose

The FDA has required that Solius complete a clinical study with statistical significance to demonstrate that the Solius device can safely treat vitamin D insufficiency or deficiency.

4 Objectives

4.1 Study endpoint

The endpoint is to improve vitamin D status in the treatment group compared to sham controls. We expect at least 70% of vitamin D deficient/insufficient subjects in the treatment group to convert to insufficient/ sufficient. Also, because of seasonal variations and other confounders, we expect maximum 30% of subject convert to insufficient/sufficient in sham control group.

Study Outcome Measures

Improvement of serum concentrations of 25(OH)D will be measured by 25(OH)D analysis at baseline, each month and the end of the study. Serum 25(OH)D levels will be determined using the Liquid Chromatography with tandem mass spectrometry (LC/MS/MS) method.

4.1.1 Endpoint Measures

1. At each visit, the subjects will be asked to report any adverse events and any skin changes. These adverse events will be tabulated and reported at the study completion.
2. Blood samples will be obtained all subjects (case and control) monthly at various stages throughout the 5-week titration and 16-week intervention. Blood samples will be obtained once a week for 4 weeks after the 16-week intervention. Baseline samples will be obtained immediately preceding the first UVB exposure. Blood samples will be sent to the Quest Diagnostics for determining the serum 25(OH)D levels. An additional tube of blood will be collected for future study at week 1, week 5, week 13, week 21 and week 25.

5 Study Design

This is a double-blinded sham control clinical trial seeking to determine the safety and efficacy of the Solius Photobiologic System in increasing the serum concentrations of 25(OH)D in a vitamin D deficient/insufficient adult population. We will make our best effort to recruit individuals with all Fitzpatrick skin types as requested by the FDA. The study will be conducted at Boston University after it is approved by Boston University's Institutional Review Board.

Table 1. The below guidelines will be used to make this distinction:

Table 1: Fitzpatrick Skin Types

Skin type	Typical Features	Tanning ability
I	Pale white skin, blue/green eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

Each subject will be categorized into one of 6 Fitzpatrick skin types, type I, II III, IV and skin type V or VI. Skin types V and VI will be combined to represent the group with the darkest skin tone for subgroup analysis.

A total of 80 adult subjects with 5 skin types groups (I, II, III, IV and V/ VI) will be enrolled for vitamin D deficiency/ insufficiency screening. The screening test for 25(OH)D will be performed by the Boston Medical Center's clinical laboratory for local Quest diagnostic laboratory which is able to perform the test within 24 hours. We expect at least 80% of the population in the Boston area has a level of 25(OH)D

below 30 ng/ml. Thus, we expect to enroll approximately 100 subjects with different group skin types to enroll 80 vitamin D deficient or insufficient subjects in this study. The research coordinator will be responsible for randomization and allocation. Thus, the study will be blinded to other members of the research team. Solius and the PI will have no contact with the participants. Subjects will be selected to or not to receive the UVB intervention (40 subjects in the treatment group and 40 subjects in the control group) (Figure 1). Two study groups will be matched by age, sex, BMI, and skin type by stratified randomization.

The device will have a strip of blue/purple colored LEDs installed inside the device. For users that are defined in the treatment group, both UVB lamps and blue/purple colored LEDs will turn on during the treatment. For users that are defined in the control group, they will go through the same pre-treatment workflow. However, when the user hits start treatment program in the device, only the blue/purple LEDs will turn on instead of the UV lamps, which emit radiation that is not visible to the naked eye.

Blood samples that will be obtained at the screening visit will be sent to either BMC's clinical laboratory or a local Quest laboratory for a 24 hour turnaround to determine eligibility of each participant. All blood samples collected monthly during the intervention and weekly after the intervention will be sent to Quest Diagnostics for measurement of serum concentrations of 25(OH)D by liquid chromatography with tandem mass spectrometry analysis as requested as requested by the FDA. The study design is summarized in Figure 1 and Table 2. As shown in the Table 2, blood samples will be collected at the screening visit, during the intervention period (week 1, week 5, week 9, week 13, week 17 and week 21). As requested by the FDA, we will also obtain blood sample after the intervention (week 22 – 25). We will collect an additional tube of blood for future study at week 1, week 5, week 13, week 21 and week 25.

Figure 1. Summary of protocol: Evaluating the effect of the Solius Photobiologic System in improving vitamin status in adults

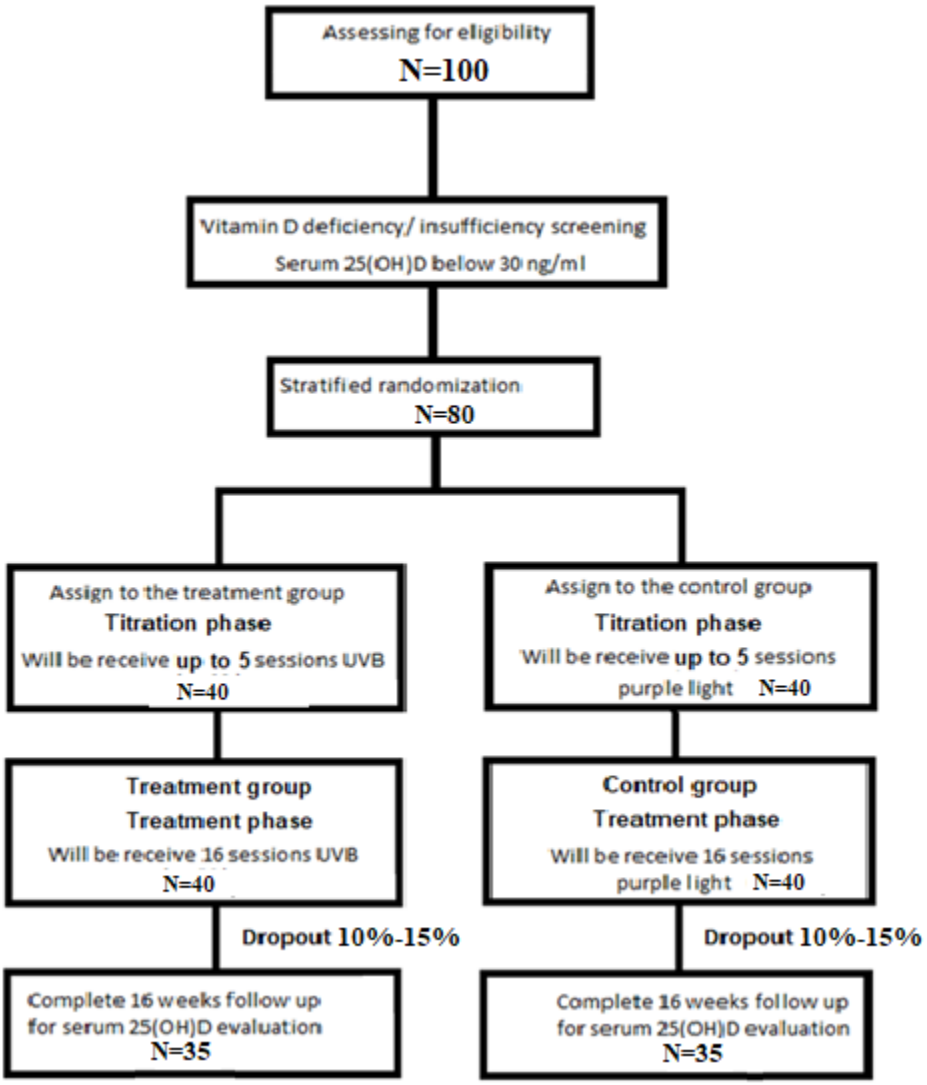


Table 2. Outcomes measurement at each time point of the study for both study groups

Activity	Screening	Titration					Intervention															
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18	Wk 19	Wk 20	Wk 21
Informed Consent	X																					
Inclusion/Exclusion	X																					
Medical History	X																					
Demographics/ Skin typing	X																					
UVB Exposure/sham exposure		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
25(OH)D	X	X				X				X				X				X				X
Additional blood						X								X								X
Sun exposure/ Vit. D food checklist	X					X				X				X				X				X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Activity	Post-intervention			
	Wk 22	Wk 23	Wk 24	Wk 25
Informed Consent				
Inclusion/Exclusion				
Medical History				
Demographics/ Skin typing				
UVB Exposure/sham exposure				
25(OH)D	X	X	X	X
Sun exposure/ Vit. D food checklist				X
Concomitant Medications	X	X	X	X
Adverse Events	X	X	X	X

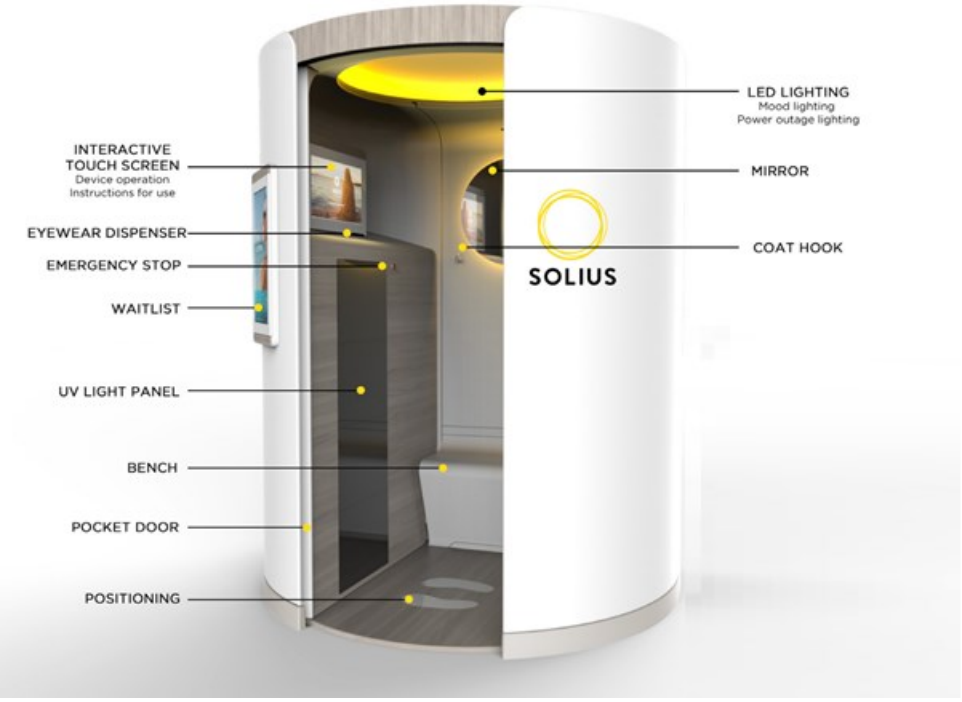
6 Potential Risks and Benefits

6.1 Risks

The main acute adverse effects of narrowband UVB (NB-UVB) are erythema and induction of photosensitivity diseases, such as polymorphic light eruption (PLE). Although the risk of erythemal episodes may be increased by concomitant phototoxic drugs[14,15], this can be minimized by undertaking a baseline minimal erythema dose (MED) and establishing treatment protocols based on an individual's MED[16]. This also allows any unsuspected abnormal photosensitivity diseases to be detected, in particular solar urticaria or chronic actinic dermatitis (CAD). Induction of PLE may occur during a treatment course but generally can be accommodated via dose adjustments and judicious use of topical corticosteroid, without the need to stop NB-UVB[17]. Other uncommon side-effects, such as psoriatic lesional blistering, occasionally occur but generally treatment is very well-tolerated[18,19].

Overexposure to our artificial UVB source may incur similar symptoms to a mild sunburn (slight reddish coloration to the skin). The Solius Photobiological System was designed to minimize total UVB exposure to minimize the potential for sunburn. To make sure subjects do not develop redness (erythema) or blistering, the exposure will set for the lamp to 60% or 0.60 of the minimal erythemal dose (MED) for each individuals' skin type.

Over exposure to the UVB to the eyes may cause photokeratitis. To prevent the overexposure, the subject's dosage will be determined during titration period. Eye protection will be provided to the subject in the device before each treatment. The device software will require that the subject physically obtained the eye protection from the dispenser in the device before the device can be turned on to emit the UVB light. An additional safety feature of the device is the height of the emitting lens is 51". Testing conducted by 3rd party showed that there is almost 0 UV output at 56" from the floor. Thus, little or no radiation is emitted above the height of 5 feet and therefore the face and eyes will not be exposed to the UVB light if for some reason the subject does physically place the eye protection shield over his/her eyes. This is demonstrated in the enclosed picture of the device along with its other features.



The UV light panel height is 51 inches.

As the appropriate doses are individualized to the subject, to establish the correct dose, each subject will complete a titration period of up to 5 weeks. The titration period will start with an erythemally weighted dose of 10.53 mJ/cm2 to 43.07 mJ/cm2 (depending on skin type) and increase by 26 – 36% each step until a maximum erythemally weighted dose of 34.88 mJ/cm2 – 109.33 mJ/cm2 (depending on skin type). If the subject shows a skin reaction i.e erythema, the dose will be reduced to 60% of the dose that caused the skin reaction/erythema.

The subject's dosage will be administered under conditions of full-body exposure except the face (males in swimming trunks or briefs and females in bikini or bra and panties) of 0.6 minimal erythemal dose (MED) once per week for 16 weeks. At each visit, the subject will report adverse events and any skin changes.

The PI will be available to the study staff member to answer any questions or concerns from potential subjects prior to consenting. We will have the blood samples drawn by trained professionals to minimize the risk of hematoma formation, bleeding, or infection at the site of needle insertion. Study staff will update subjects in a timely way on any new information that may affect their health, welfare, or decision to stay in this study. Any and all side effects reported will be recorded in the subjects' file in the study binder. Subjects will be instructed to call the study staff immediately if any side effects do occur. The PI will advise the study staff who have received the information from the subject as to how this side effect should be handled, recorded and reported. After the determination, all samples will be de-identified. We have a plan to protect subject privacy and confidentiality, which is explained in the plan to protect subject privacy and confidentiality in the data section.

Vitamin D deficiency and insufficiency is common in adults due to an inadequate dietary intake of vitamin D and or inadequate sun exposure. Chronic (years to decades) vitamin D deficiency and insufficiency can lead to bone loss resulting in increased risk of fracture later in life. Chronic vitamin D

deficiency can also cause a mineralization defect of the skeleton resulting in osteomalacia. Short term (6 months) vitamin D deficiency and insufficiency is not associated with significant bone loss or osteomalacia. Therefore, the participants, especially those who are in the sham treatment group, are at no increased risk for fracture or osteomalacia. At the termination of this study those participants who were in the sham group will be encouraged to take a vitamin D supplement along the guidelines recommended by the Endocrine Society to correct their vitamin D deficiency and insufficiency.

Chronic excessive exposure to sunlight or ultraviolet radiation for prolonged periods of time, in years or decades, can increase risk for nonmelanoma skin cancer. To minimize the risk the subjects will be 22 years and older and will be exposed to suberythemal doses of UVB radiation for the duration of the study

6.2 Potential Benefits

The study participants may receive no benefit. All participants in the study will know that they are vitamin D deficient/ insufficient because that will be a requirement for being enrolled in the study. The control group will only know their vitamin D status and will receive no additional benefit for participating in the study. The group exposed to the Solius Photobiological System's UVB light may improve their vitamin D status because the UVB emitting lamps are designed for producing vitamin D in the skin similar to sunlight. Results from this study will provide scientific knowledge regarding this devices ability to produce vitamin D and improve vitamin D status in people with vitamin D deficiency such as subjects with fat-malabsorption syndromes. All subjects will be evaluated for vitamin D deficiency/insufficiency at the end of study and subjects with vitamin D deficiency/insufficiency will be advised to take a vitamin D supplement along the guidelines recommended by the Endocrine Society Practice Guidelines on Vitamin D. Alternatively, if they do not wish to take a supplement and would like a prescription for vitamin D we will contact their primary care doctor and inform them of their vitamin D status so that they can prescribe the appropriate vitamin D treatment as recommended by the Endocrine Society's Practice Guidelines on Vitamin D.

Subjects will not be responsible for any research related costs. They will receive compensation in each of their visit, which is shown below. Parking vouchers or transportation cost are available for each visit.

Study group/activity	Post-intervention				Total	
	Wk 22	Wk 23	Wk 24	Wk 25		
Activity (both treatment group and sham control group)	BD	BD	BD	BD	$1550	Up to 2,330
Compensation	$50	$50	$50	$250		
Transportation cost up to	PV or up	PV or up	PV or up	PV or up to $30	Up to $780	

Study group/activity	Screening visit	Titration					Intervention															
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18	Wk 19	Wk 20	Wk 21
Activity (both treatment group and sham control group)	Screening Consent BD	UV	UV	UV	UV	UV BD	UV	UV	UV	UV BD	UV	UV	UV	UV BD	UV	UV	UV	UV BD	UV	UV	UV	UV BD
Compensation	$100	$50	$50	$50	$50	$50	$50	$50	$50	$50	$50	$50	$50	$50	$50	$50	$50	$50	$50	$50	$50	$50
Transportation cost up to	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30	PV or up to $30

Note: BD: Blood draw; UV: Ultraviolet B radiation exposure or sham control
Blood samples will be collected after each UV exposure.

6.3 Analysis of Risks in Relation to Benefits

Highly trained professionals will be performing the blood draws which is likely to be a chance of risk. The adverse skin reaction from the Solius Photobiological System such as skin erythema and pruritus is a possible risk in this study. However, this study will expose the participants to a relatively low intensity of UVB (0.6 MED), so the risk of adverse reaction is minimal. All the participants will be asked for their willingness to receive the intervention at every exposure and will be questioned and examined for any potential adverse reaction due to the intervention. If any significant adverse reaction is detected, the intervention will immediately stop and the affected participant will receive immediate medical attention. Significant adverse reactions include photokeratitis, moderate to severe skin tenderness, itchness and tightening, skin blistering, or bruising or tearing of skin. The risks of breach of confidentiality are highly unlikely, and therefore benefits will greatly outweigh the risks.

7 Study Subject Selection

7.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Age at least 22 years old
2. Male or Female
3. Skin Type I-VI
4. Women of child bearing potential must be on birth control and not pregnant based on a negative pregnancy test at baseline.
5. Ability and Willingness to give informed consent and comply to protocol requirements
6. Serum total 25(OH)D < 30 ng/mL

7.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Ongoing treatment with supplemental or pharmacological doses of vitamin D, vitamin D metabolites or analogues
2. Pregnant
3. History of underlying photosensitivity
4. Use of medications that cause a photosensitivity reaction (including but not limited to): tetracycline, tretinoin, amiodarone, doxycycline, naproxen, diphenhydramine, methotrexate, and hydrochlorothiazide
5. History of skin cancer
6. Plan to received significant sun exposure below the 33rd parallel during study
7. Used tanning or phototherapy devices within the last 30 days
8. Vitamin D supplement use of more than 600 IUs daily.
9. Systemic steroids use
10. H1 antihistamine use in the last 7 days
11. Diagnosed with light allergies (including but not limited to): actinic prurigo, polymorphous light eruption, or solar urticaria
12. Diagnosed with light sensitivities (including but not limited to): protoporphyria, photodermatitis, xeroderma pigmentosum, lupus erythematosus, chronic actinic dermatitis, or UV-sensitive syndrome

8 Study Intervention

The treatment group (n=40) will be exposed to the Solius Photobiological System, and the control group (n=40) will receive the same procedure with only the blue/purple LEDs. The study intervention will involve an investigational UVB emitting device, The Solius Photobiologic System created by Solius. The Solius Photobiological System emits UVB to make sure subjects do not develop redness, the exposure will set for the lamp to 60% or 0.60 of the minimal erythemal dose (MED) for each individual's skin type.

As the appropriate doses are individualized to the subject, to establish the correct dose, each subject will complete a titration period of up to 5 weeks. The titration period will start with an erythemal weighted dose of 10.53 mJ/cm2 to 43.07 mJ/cm2 (depending on skin type) and increase by 26 – 36% each step until a maximum erythemal weighted dose of 34.88 mJ/cm2 – 109.33 mJ/cm2 (depending on skin type) or the subject shows a skin reaction. This dose will be the subject's dosage.

The device will have a strip of blue/purple LEDs installed inside the light towers. For users that are defined in the treatment group, both UV lamps and purple LED will turn on during the treatment. For users that are defined in the control group, they will go through the same pre-treatment workflow. However, when the user hits start treatment, only blue/purple LEDs will turn. The times that the control subjects will be in the sham operational device mode for the titration phase and 16-week treatment phase will be the same as those in the intervention UVB device mode based on skin type.
According to a previous study by Solius where 43 subjects were exposed to a 0.6 MED, the stimulation of cutaneous vitamin D and subsequent increase in serum concentration of 25(OH)D from phototherapy was compared to the effect of a Recommended Daily Allowance (RDA) based dose of 600 IU vitamin D3 supplement daily for 10 weeks. Thus we will expose these individuals a 0.6 MED once per week for 16

weeks to observe the effect on 25(OH)D serum concentration. Serum 25(OH)D concentration will be monitored until 4 weeks after the intervention.

9 Study Procedures

We will advertise for this study at the Boston University Medical campus via email newsletters and advertisements on various TV screens. Once subjects have responded to the study flyer and contacted study staff, they will be screened over the phone to determine eligibility. This screen is anonymous and no answers will be recorded. During the preliminary anonymous screening telephone call, the subject will be asked about their medical history and inclusion/exclusion criteria. None of the answers or identifiable information will be recorded. Completion of the preliminary anonymous screening will be documented in the study binder. Once the subjects are determined to be eligible, they will be scheduled for their first visit to Boston University Medical Center's General Clinical Research Unit at 80 E. Concord St or in the clinical research space in the Vitamin D, Skin, and Bone Research Laboratory located at 85 E Newton St, M-1013 Boston, MA 02118. The study coordinator or IRB-approved research assistants will consent the subjects. Dr. Holick will not participate in consenting the subjects, but will be available to answer any questions or concerns that the subjects may have during the process. We will ask the subjects to read and ask any questions in regards to the screening process that they have prior to signing the consent form. This consent form will also allow us to perform a 25(OH)D blood screen, collect urine samples, and conduct our study experiment. Researchers will document that consent was given in our consent form log sheet where (s)he will need to sign and date that informed consent was given and that the subject received a copy of the ICF.

We plan to use sham control with doing a modification on instrument hardware and software. The research coordinator will be responsible for randomization and allocation. Thus, the study will be blinded to other members of the research team. Approximately 100 adult subjects with 5 skin types groups (I, II, III, IV and V/ VI) will be enrolled for vitamin D deficiency/ insufficiency screening. We expect at least 80% of the population in the Boston area has a level of 25(OH)D below 30 ng/ml. Thus, we will enroll approximately 100 subjects with different group skin types to enroll 80 vitamin D deficient or insufficient subjects in this study. They will be randomized to receive or not to receive the UVB intervention (40 subjects in the treatment group and 40 subjects in the control group) (Figure 1). The device will have a strip of colored LED installed inside the light towers. For users that are defined in the treatment group, both UV lamps and colored LED will turn on during the treatment. For users that are defined in the control group, they will go through the same pre-treatment workflow. However, when the user hits start treatment, only blue/purple LEDs will turn on instead of the UV lamps, which are invisible. To elaborate further, all subjects will use the same device with the exact same workflow on the touchscreen user interface. The experience in starting a SOLIUS session, answering the safety questions, automatic dispensing of eyewear, etc. will be exactly the same for active and control subjects. This is achieved by adding an independent software branch to the existing system that replicates the user workflow code but only turn on the LED drivers. LED strips are added to the existing light tower, and the lights will project through the same light path as the UV lamps. As a result, visible blue/purple light will be emitted from the same emitting window as the UV lamps. The subjects will not know if they are being actively treated or not and we will make the experience for both be virtually the same. The research coordinator who sets up the device will know only which arm the subject is assigned to (arm A or B) but will not know which arm is the treatment or control.

Blood samples that will be obtained from all participants at the screening visit will be sent to either BMC's clinical laboratory or a local Quest laboratory for a 24 hour turnaround to determine eligibility of each participant. All blood samples collected monthly during the intervention and weekly after the intervention will be sent to Quest Diagnostics for measurement of serum concentrations of 25(OH)D by liquid chromatography with tandem mass spectrometry analysis. The study design is summarized in Figure 1 and Table 2. As shown in the Table 2, blood samples will be collected at the screening visit, during the intervention period (week 1, week 5, week 9, week 13, week 17, week 21) and after the intervention (week 22 – 25). We will collect an additional tube of blood for future study at week 1, week 5, week 13, week 21 and week 25.

Each subject will be advised to come in for five titration visits. The purpose of these visits to establish the correct UVB dose in the SoliusONE device or to expose the control group for this same amount of time in the sham operated device for their skin type. At these visits, each subject will be asked questions about consumption of vitamin D, sun exposure, and whether he/she has had any adverse changes in his/her health. After the titration visit, each subject will complete a 16-week course of SoliusONE treatment or sham treatment. During each titration/treatment session, the study personnel will record subject's information in the application that is installed in the study personnel's smartphone. The information to be recorded include subject ID, age and sex. This allows the software to link to database and create user profiles for dosing. None of the identifiable information will be recorded in the application. Then, each subject will stand in the SoliusONE device while exposed to UVB light or LED visible blue/purple light. Each subject will be asked to wear a swimsuit, swimming trunks (for males) or bikini (for females) while being exposed to UVB or sham LED light in the device. The device is large enough so that the participant is able to remove their clothing and to hang it up on a hook that is provided in the device. If they are wearing their bathing suit, they will then be exposed to the UVB radiation and blue/purple light or the sham group will be exposed to only the blue/purple light . If they have brought their bathing suit with them, they will be able to put it on in the device and then be exposed to the UVB light. They then have the option of keeping the bathing suit on and dressing or removing the bathing suit and putting on all of their undergarments and clothing before exiting the device. For those who either do not want to wear a bathing suit under their clothing or have forgot to bring their bathing suit then they will have the option of being exposed to the UVB in their underwear (males in their underwear shorts and females in their panties and bra). Each session will take approximately 2-10 minutes depending on the subject's skin type group (lighter skin type groups require less treatment time). Before and after each treatment, the device will be cleaned using disinfectant to ensure proper hygiene.

Blood samples will be obtained from all subjects (cases and controls) at the screening visit and monthly throughout the 16 weeks of the study duration (weeks 1, 5, 9, 13, 17, 21), and weekly after the 16-week intervention for 4 weeks (week 22 – 25). Blood samples will be sent to Quest Diagnostics for determining the serum 25(OH)D levels. The study design summarized in Figure 1 and Table 2

If a subject needs to end his/her regiment early they will be able to do so, with no change to the study procedure. We will require a final blood sample collection from the study subject prior to his/her removal.

We anticipate the entire study will take 12 months to complete 16-week treatment for case group. As discussed earlier the study subject's involvement will last 26 weeks from screening to completion include one week for screening, 5 weeks for titration, 16 weeks for treatment and 4 weeks of post-treatment serum 25(OH)D monitoring.

10 Assessment of Safety and Data Safety Monitoring Plan (DSMP)

10.1 Definitions

The following definitions will be used in the assessment of safety:

Adverse Event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Serious Adverse Event (SAE) is any adverse event that

(1) results in death;
(2) is life-threatening;
(3) results in subject hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;
(5) results in a congenital anomaly/birth defect;
(6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Life-threatening means that the event places the subject at immediate risk of death from the event as it occurred.

Unanticipated Problem is defined as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected; AND
- is related or possibly related to participation in the research; AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

10.2 Safety Review

Dr. Shirvani or Dr. Charoenngam will interview the subjects in the intervention and sham groups before their next exposure each week for any adverse events including erythema or any other skin reactions. At the time of the evaluation, it will be determined whether the subject will continue with the next exposure or whether the subject will be removed from the study. This will be based on the determination of the degree of erythema or adverse skin reaction.

In addition, Prior to each treatment, Solius software will prompt the user with the following questions to assess erythema:

1. Did you observe any pinkness (similar to sunburn) after your last treatment? (yes / no)
2. Did the pinkness last for more than 3 days? (yes / no)
3. Did you experience any pain or discomfort (excluding itch) with the pinkness? (none / mild / moderate/ severe)

Based on the user's response, the software could maintain current dose, reduce dose, or block account for further investigation. The PI or Dr. Shirvani or Dr. Charoenngam will be notified to perform further assessment if an account was blocked by the software.

The following known side effects of UVB will be monitored:

Side effect	**Signs/symptoms**	**Instruction for subjects on monitoring**
Sunburn	Pain, tenderness of the skin, redness, tightness, itching, and rarely blistering	Check for pain and redness 4-6 hours after treatment. If there is severe pain, should seek medical attention. If there are blisters, should seek medical attention
Photoaging	Atrophic skin, coarseness, fibrotic areas, increased fragility, laxity, mottled pigmentation, telangiectasias, wrinkling	If there is increased fragility (i.e. easy bruising or tearing of skin), then should seek medical attention. The other photoaging side effects are benign and more of a cosmetic nature.
Tanning	Skin darkening	As a benign side effect, no subject monitoring is needed

10.3 Reporting Plans

Dr. Alan Farwell will serve as an Independent Scientific Reviewer (ISR). He will provide an assurance that the findings and conclusions reached are supported by the data presented, and also, to assure that the content is consistent with applicable scientific standards and will be responsible for a review of the data analysis, data interpretation and/or presentations and manuscripts.

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems, safety monitors' reports, and Adverse Events to the BMC/BU Medical Center IRB in accordance with IRB policies:

- Unanticipated Problems occurring at BMC/BU Medical Campus involving a fatal or life-threatening event will be reported to the IRB within 2 days of the investigator learning of the event.
- Unanticipated Problems occurring at BMC/BU Medical Campus not involving a fatal or life-threatening event will be reported to the IRB within 7 days of the investigator learning of the event.
- Reports from safety monitors with recommended changes will be reported to the IRB within 7 days of the investigator receiving the report.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.
- Reports from safety monitors with no recommended changes will be reported to the IRB at the time of continuing review.

10.4 Stopping Rules

A subject will be withdrawn from the study if refuse to participate, or if the subject undergoes an adverse reaction to the light source e.g. skin erythema or pruritus.

11 Data Handling and Record Keeping

11.1 Confidentiality

Subjects are assigned a code after consent and enrolled in the study. All coded records containing subject information will be stored in Dr. Holick's offices under lock and key. The blood samples will be kept in the Dr. Holick lab (M-1011). The door to the Vitamin D lab is accessed by those who have ID access to the lab. The data will be coded and after 7 years will be deidentified and kept indefinitely. Electronic information will be stored on a departmental server ("Y"drive) and "C" drive of study coordinator's computer both of which are password protected. Paper records will be stored in a locked room for which only study staff will have access to. Master list will be stored on the study coordinator's PC and will not be stored with study data. All other electronic data will be on the PC of the study coordinator, which is password protected. Paper master list will be stored and locked in M1013; only study staff and study coordinator have access to this room. All locations where data will be kept are inaccessible to the public. Data will be available only to study personnel. Data will be kept in a locked room. Study code will be used for all study data that is collected. The study coordinator and study staff will keep the subject list on their computer, which is password accessible only.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

11.2 Source Documents

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. Data may be transcribed legibly on CRFs supplied for each subject or directly inputted into an electronic system or any combination thereof.

11.3 Case Report Forms

The study case report form (CRF) will be the primary data collection instrument for the study. All data requested on the CRF will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, “N/D” will be written. If the item is not applicable to the individual case, “N/A” will be written. All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data will be entered above it. All such changes will be initialed and dated. There will be no erasures or white-out on CRFs. For clarification of illegible or uncertain entries, the clarification will be printed above the item, then initialed and dated.

See the Appendix for the following CRFs: Study Visit Report Form

11.4 Study Records Retention

All coded records containing subject information will be stored in Dr. Holick’s offices under lock and key. The blood will be kept in the Dr. Holick lab (M-1021A). The door to the Vitamin D lab is accessed by those who have ID access to the lab. The blood samples and data will be de-identified and kept indefinitely. They may be used for possible additional research in the future. Electronic information will be stored on a departmental server ("Y"drive) and "C" drive of study coordinator's computer both of which are password protected. Paper records will be stored in a locked room for which only study staff will have access to. Master list will be stored on the study coordinator’s PC and will not be stored with study data. All other electronic data will be on the PC of the study coordinator, which is password protected. Paper master list will be stored and locked in M1013; only study staff and study coordinator have access to this room. All locations where data will be kept are inaccessible to the public. Data will be available only to study personnel. Data will be kept in a locked room. Study code will be used for all study data that is collected. The study coordinator and study staff will keep the subject list on their computer, which is password accessible only. Study records will be retained for at least seven years after completion of the study. Documentation of informed consent of subjects will be retained for at least seven years after the study is closed, unless the IRB waived the requirement for informed consent or documentation of informed consent. Such records may be preserved in hardcopy, electronic or other media forms and must be accessible for inspection and copying by authorized individuals.

12 Statistical Plan

The endpoint is the difference in vitamin D insufficiency/sufficiency prevalence between the treatment and the control group use at 16 weeks of follow-up. The subject will have at least one serum 25(OH)D

evaluation within 16 weeks, and at least one phototherapy session in the 16 weeks follow up. The protocol includes a sample size calculation, which allowed for a loss to follow-up of 15%.

Statistical analysis will be performed using SPSS Statistics, version 25 (IBM Corporation). Age, sex, BMI, and Fitzpatrick skin type will be matched in two study groups. Two-sided $P < .05$ will be considered significant. All models will be developed according to the intention-to-treat principle. A supportive analysis will also be conducted on the per-protocol (PP) population.

The biological and clinical characteristics at enrolment will be presented, and all variables for the participants in the treatment and control groups will be compared at each follow-up using Fisher's exact test for categorical variables and a Mann–Whitney *U* test for continuous variables. For intergroup differences, 95% CIs will be also calculated. The endpoint, the proportion of subjects converting from vitamin D deficiency/insufficiency to vitamin D insufficiency/sufficiency at 16 weeks will be compared between groups using Fisher's exact test and logistic regression adjusting for skin types. Secondary analysis will be involved a comparison of changing in serum levels of 25(OH)D between groups using a Mann–Whitney *U* test and linear regression adjusting for skin types. A linear mixed model will be used to examine the relationship between phototherapy and serum $25(OH)D_3$ at different time points, adjusting for the baseline values and correlation of outcomes within individuals and season.

12.1 Study Hypotheses

We suspect that with the incorporation of a 16-week phototherapy regiment, at least 70% of vitamin D deficient/insufficient subjects in the treatment group will convert to insufficient/ sufficient. Also, because of seasonal variations and other confounders, we expect a maximum 30% of the subjects to convert to insufficient/sufficient in sham control. In particular, we expect individuals with Fitzpatrick Type I and II skin to show the greatest response to phototherapy.

12.2 Sample Size Determination

The endpoint of this study is to compare the improvement of vitamin D status between treatment group and the controls. A previous study by Chandra et al. demonstrated the increase in the mean serum 25(OH)D in subjects with malabsorption syndrome receiving UV therapy from 21± 3 ng/mL to 27±4 ng/mL after 8 weeks (13). We would expect that to increase the serum 25(OH)D level by 10 ng/mL (SD=5ng/ml), after 16 weeks based on a previous study (13) as well as an earlier pilot study that was completed by Solius.

The endpoint is to improve vitamin D status in the treatment group compared to sham controls. We expect that the serum levels of 25(OH)D will increase more than 10 ng/ml (SD=5ng/ml) after 16 weeks of intervention in the treatment group compared to controls. Subjects converted from vitamin D deficient/insufficient to insufficient/sufficient is considered a minimum clinical important difference (MCID). We expect at least 70% of vitamin D deficient/insufficient subjects in the treatment group to convert to insufficient/ sufficient. Also, because of seasonal variations and other confounders, we expect maximum 30% of subject convert to insufficient/sufficient in sham control.
With the desired power of 80% and significance level (α) of 0.01, the sample size in each group is 35.

Approximately 100 adult subjects with 5 skin types group (I, II, III, IV and V/ VI) will be enrolled for vitamin D deficiency/ insufficiency screening. We expect that at least 80% of the population in the

Boston area has a level of 25(OH)D below 30 ng/ml. Thus, we will enroll 100 subjects with different skin types to enroll 80 vitamin D deficient or insufficient subjects in this study. We plan to match treatment and control group for age, sex, BMI and skin type by stratified random sampling (40 subjects in each group). In our experience, the rate of screen failure and subject dropout is 10-15%. Then, we expect to have at least 35 subjects per each group.

Parameters	**Value**
Conversion of the subjects from vitamin D deficient to vitamin D insufficient/sufficient or vitamin D insufficient to vitamin D sufficient in the treatment group after 16 weeks (P1)	70%
Conversion of the subjects from vitamin D deficient to vitamin D insufficient/sufficient or vitamin D insufficient to vitamin D sufficient in the control group after 16 weeks (P2)	30%
Significant level	0.01
Power	80%

$$N_1 = \left\{ z_{1-\alpha/2} * \sqrt{\bar{p} * \bar{q} * (1 + \frac{1}{k})} + z_{1-\beta} * \sqrt{p_1 * q_1 + (\frac{p_2 * q_2}{k})} \right\}^2 / \Delta^2$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + k p_2}{1 + K}$$

$$\bar{q} = 1 - \bar{p}$$

$$N_1 = \left\{ 2.58 * \sqrt{0.5 * 0.5 * (1 + \frac{1}{1})} + 0.84 * \sqrt{0.7 * 0.3 + (\frac{0.3 * 0.7}{1})} \right\}^2 / 0.4^2$$

$$N_1 = 35$$

$$N_2 = K * N_1 = 35$$

p_1, p_2 = proportion (incidence) of groups #1 and #2
$\Delta = |p_2 - p_1|$ = absolute difference between two proportions
n_1 = sample size for group #1
n_2 = sample size for group #2
α = probability of type I error
β = probability of type II error
z = critical Z value for a given α or β
K = ratio of sample size for group #2 to group #1

The research coordinator will be responsible for randomization and allocation. Thus, the study will be blinded to other members of the research team. We expect that the serum levels of 25(OH)D will increase by at least 10 ng/ml in the treatment group compared to the control group after 16 weeks UV exposure in a linear fashion. We will do an assessment every four weeks, expecting that there will be a minimum of 2.5 ng/ml increase in the serum 25(OH)D. We will conduct the blinded interim analyses to re-assess the planned sample size after thirty five subjects in each group have completed four weeks of

intervention by an independent statistician. The sample size adjustment will be made to ensure the appropriate power to determine the effect of UV exposure on vitamin D synthesis.

13 Ethics/Protection of Human Subjects

This study is to be conducted according to applicable US federal regulations and institutional policies (which are based in federal regulations, guidance, and ICH Good Clinical Practice guidelines).

This protocol and any amendments will be submitted to the Boston Medical Center and Boston University Medical Campus IRB, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. Consent will be documented as required by the IRB.

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