Trial/Study Protocol

FULL/LONG TITLE OF THE TRIAL

Determining reference ranges for a novel Light Emitting Diode (LED) phototest device

Trial/Study Acronym	LED-REF
Sponsor	University of Dundee
Sponsor Ref Number	2-003-24
Funder	British Skin Foundation
Chief Investigator	Professor Sally H. Ibbotson
IRAS Number	335176
REC Number	24/NI/0138
Public registry ID Number	researchregistry9666
Version Number and Date	V1 19/08/2024

- This protocol has regard for the HRA guidance and order of content

SIGNATURE PAGE

Signatures

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature:

..... Date: ...../...../.....

Name (please print): .....

Position: .....

Chief Investigator:

Signature: ..... Date: ...../...../.....

Name: (please print): Professor Sally H. Ibbotson

(Optional)

Statistician:

Signature: .....

Name: (please print): Robert Dawe

Position: Consultant Dermatologist

KEY TRIAL/STUDY CONTACTS

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LIST OF ABBREVIATIONS

AE	Adverse Events
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Scheme
CRF	Case Report Form
GP	General Practitioner
HRA	Health Research Agency
LED	Light Emitting Diode
MED	Minimal Erythema Dose
NB	Narrowband
NHS	National Health Service
NRD	No Response Dose
PIS	Participant Information Sheet
QC	Quality Control
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TASC	Tayside Medical Science Centre
TMF	Trial Master File
TMG	Trial Management Group
UK	United Kingdom
UV	Ultraviolet
UVA	Ultraviolet-A
UVB	Ultraviolet-B
UVR	Ultraviolet Radiation

SUMMARY/SYNOPSIS

Trial Title	Determining reference ranges for a novel LED phototest device	
Trial Design	Preliminary observational dose-ranging study	
Trial Population	Healthy adult volunteers	
Sample Size	50 participants (40 Fitzpatrick Skin Type I – III, 10 Fitzpatrick Skin Type IV – VI)	
Planned Trial/study Period	12 months	
Clinical phase duration	Participants expected to be in the study for 3 days (excluding screening visit) with a potential for a 4th day if no erythema induced on first study day.	
Follow up phase duration	No follow-up	
Primary	Objectives To establish a normal range of erythemal sensitivity in healthy volunteers for the developed LED-based phototest device.	Outcome Measures Semi-quantitative visual scoring of erythema. Reflectance measurements of skin colour if no visual erythema observed.
Secondary	Objectives To compare erythemal sensitivity between the developed LED-based phototest device and an irradiation monochromator, which is the current diagnostic equipment used in routine practice.	Outcome Measures Semi-quantitative visual scoring of erythema. Reflectance measurements of skin colour if no visual erythema observed
Inclusion Criteria	1. Healthy persons with no clinically significant abnormality identified by participant reported medical history, in particular no evidence of abnormal photosensitivity. 2. Adult males and females, >18 years only 3. Capable of giving informed consent 4. Able to understand and comply with protocol requirements and timetables, instructions and protocol-stated restrictions.	

Exclusion Criteria	1. Any photosensitising medication or supplement (systemic or topically applied to the test area) within 14 days prior to testing. 2. Insufficient clear, untanned, unaffected skin on the back to allow MED (Minimal Erythema Dose) testing. 3. Participation in a clinical study involving administration of an investigational drug (new chemical entity / non-licenced drug) or in a clinical study involving administration of a marketed drug within the past three months. 4. Known to have abnormal photosensitivity 5. Pregnant or breastfeeding 6. Use of self-tanning products on the back (test area) in the preceding 2 weeks 7. Sunbed exposure or natural sunlight-induced sunburn or tan on the back (test area) acquired within the four weeks prior to recruitment 8. Immunosuppression due to medications (such as organ transplant recipient) or disease (including HIV or haematological malignancy) 9. History of skin cancer, not including Basal Cell Carcinoma (BCC) 10. History of malignancy not curatively treated at least five years before screening visit, with exception of BCC or cervical carcinoma in situ, which may have been curatively treated within one year. 11. History of current use of illegal or 'recreational' drugs 12. Any condition which, in the opinion of the investigator, might put the subject at risk by participating in this study

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN

British Skin Foundation, 4 Fitzroy Square, London, W1T 5HQ.	£75,197 for both the development of the LED device and subsequent in-vivo study.

ROLE OF TRIAL SPONSOR AND FUNDER

Sponsor: University of Dundee

The roles and responsibilities of the Sponsor and Funder are detailed in the Letter of Award of the 4th January 2019.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

The trial will be co-ordinated by a Trial Management Group, consisting of the CI, Trial Technologist, Research Nurse, Trial Co-ordinator and Trial Manager who will meet on a monthly basis. The TMG will also be responsible for oversight of data monitoring.

PROTOCOL CONTRIBUTORS

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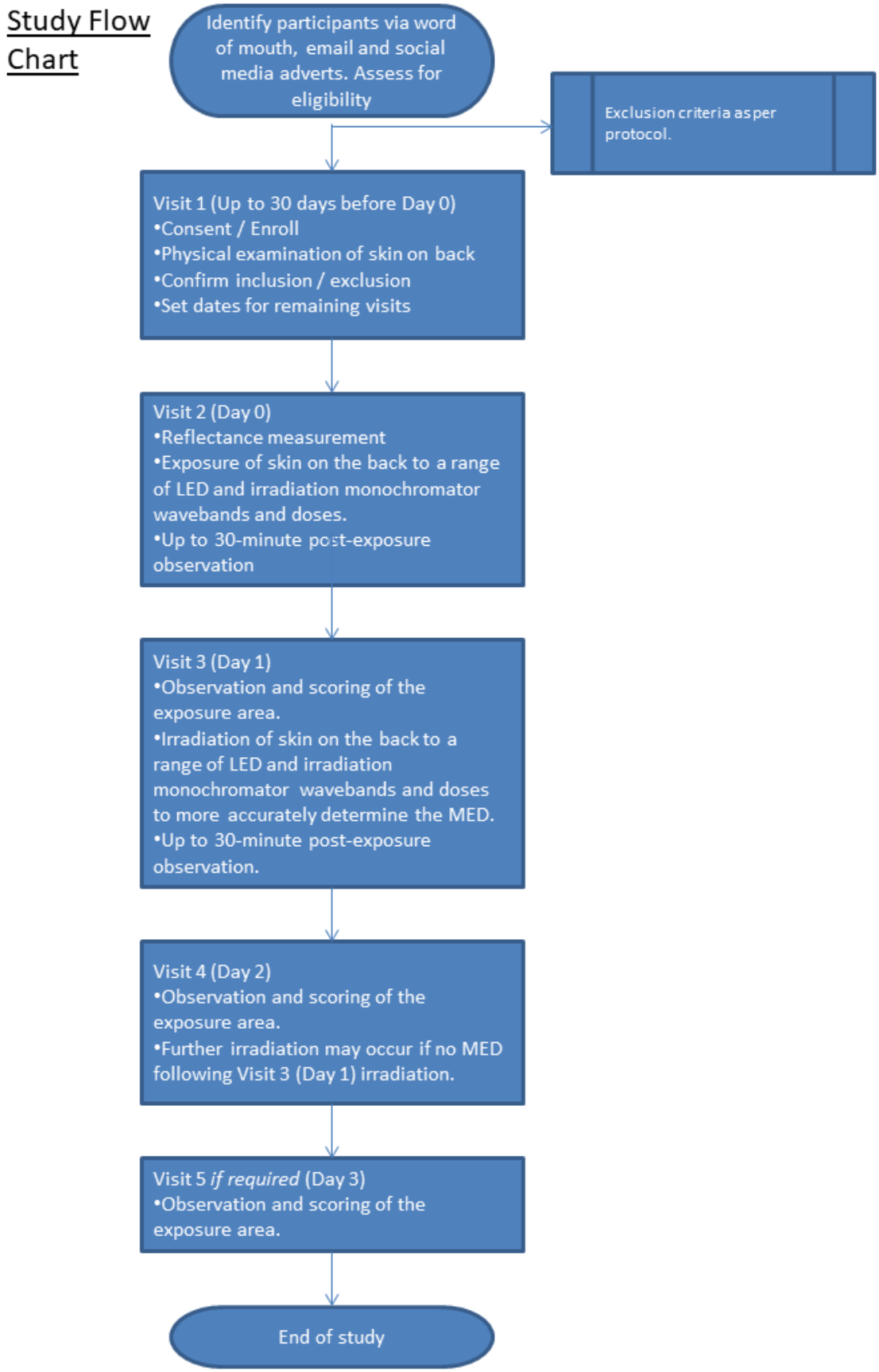
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KEY WORDS

Light Emitting Diode, Phototest, Erythema, Photosensitivity, minimal erythema dose (MED)

TRIAL FLOW CHART



1. BACKGROUND

Irradiation monochromators are devices used in the Photobiology Unit to measure the sensitivity of skin to ultraviolet (UV) and visible radiation. Erythema is the perceptible reddening of the skin that occurs following exposure to UV and visible radiation. It is caused by increased blood flow within the dermis and is an observable component of an inflammatory response. The minimal erythema dose (MED) is defined as the lowest dose of radiation to produce an erythema response that is just perceptible to the naked eye. Its measurement is accomplished by exposing several skin test sites to increasing doses of a specific waveband of irradiation. The MED at several wavebands may be established in this way. Thus, by determining the MEDs at wavebands across the solar spectrum, we can use these objective measurements as an indicator of individual sensitivity to UV and visible light.

The monochromators currently in use are custom-built Bentham monochromators (Bentham Instruments, Reading, UK). These monochromators are based on a double monochromator design, whereby specific wavebands of light are selected from the output of a broadband xenon arc lamp. These devices deliver one dose or waveband of light after another in sequence, resulting in a total exposure time of up to 2.5 hours for a full photosensitivity diagnostic test, depending on the number of exposures required.

2. RATIONALE FOR STUDY

To reduce the burden on patient and clinic time, we developed an LED-based phototesting device at Ninewells Hospital & Medical School, which was the initial part of this current British Skin Foundation-funded research project. This device is capable of delivering all required doses in parallel, therefore reducing the required time for testing (Appendix: Technical File for LED Phototest Device).

The new LED-based phototest device comprises 36 LEDs individually coupled to optical fibres, which are fixed to the skin via a custom designed fibre end piece. The LEDs are housed in a temperature-controlled enclosure, with the optical fibres exiting through an opening in the enclosure. Each LED may be individually operated via custom built control software. A custom routine can be set up in the program to control all LEDs independently yet in tandem, such that each LED delivers a specific dose of UV or visible radiation at the representative waveband. The fibre end piece is designed to take light from an optical fibre via SMA connection and deliver light through an 8 mm diameter aperture.

The Technical File for the LED-based phototest device is contained in the Appendices. As this is an in-house manufacture of a medical device, and we have no intention at this stage of commercialising

the LED-based phototest device, we have confirmation that a formal application to MHRA via IRAS is not required (Appendix: Notification to MHRA Devices Flowchart).

It is essential that before this new device is used in routine clinical practice, a normal range of erythemal sensitivity data for this device is established in healthy volunteers for the wavebands to be investigated.

Historically erythemal sensitivity has been investigated in the most UV sensitive Fitzpatrick Skin Types I & II, which are typically white skinned individuals. With a diverse population it is important that we determine normal UV sensitivity ranges for all skin colours and therefore one objective of the study is to ensure that we include participants of higher Skin Phototypes IV to VI (Appendix: Fitzpatrick Skin Type).

3. TRIAL STUDY OBJECTIVES & OUTCOMES

This study will investigate the visual effect of skin exposure to UV and visible LEDs to establish a normal range of erythemal sensitivity in healthy volunteers. It will also investigate how this erythemal sensitivity compares to the volunteer's erythemal sensitivity as determined by the current standard irradiation monochromator technique.

Table 1: Primary Objectives and Outcome Measures

Primary Objective:	**Outcome Measure:**	**Timepoint of outcome measured**
To establish a normal non-photosensitive range of erythemal sensitivity in healthy volunteers for the developed LED-based phototest device	Semi-quantitative visual scoring of erythema. Reflectance measurements of skin colour if no visual erythema observed	*Assessed at 24±2 hours after exposure*

Table 2: Secondary Objectives and Outcome Measures

Primary Objective:	**Outcome Measure:**	**Timepoint of outcome measured**
To compare erythemal sensitivity between the developed LED-based phototest device and an irradiation monochromator, which is the current diagnostic equipment used in routine practice.	Semi-quantitative visual scoring of erythema. Reflectance measurements of skin colour if no visual erythema observed	*Assessed at 24±2 hours after exposure*

4. TRIAL/STUDY DESIGN

Preliminary observational dose-ranging study to determine the typical range for erythema induction in participants with normal light sensitivity, using the developed LED-based phototest device.

Our exclusion criteria aim to exclude any volunteer with a history of abnormal light sensitivity.

5. TRIAL SETTING

The trial will take place at the Photobiology Unit at Ninewells Hospital and Medical School in Dundee. The Photobiology Unit hosts the Scottish Photobiology Service and has a leading role in the Scottish Managed Clinical Network for UV-based phototherapies (PHOTONET) and thus has high level multidisciplinary expertise in photodiagnosis and in the application of diagnostic and therapeutic uses of ultraviolet and visible light for skin diseases.

6. ELIGIBILIGY CRITERIA

6.1. Inclusion Criteria

1. Healthy persons with no clinically significant abnormality identified by participant reported medical history, in particular no evidence of abnormal photosensitivity.
2. Adult males and females, >18 years only
3. Capable of giving informed consent
4. Able to understand and comply with protocol requirements and timetables, instructions and protocol-stated restrictions.

6.2. Exclusion Criteria

1. Any photosensitising medication or supplement (systemic or topical medication applied to test area) within 14 days prior to testing.
2. Insufficient clear, untanned, unaffected skin on the back to allow MED testing.
3. Participation in a clinical study involving administration of an investigational drug (new chemical entity / non-licenced drug) or in a clinical study involving administration of a marketed drug within the past three months.
4. Known to have abnormal photosensitivity
5. Pregnant or breastfeeding
6. Use of self-tanning products on the back (test area) in the preceding 2 weeks
7. Sunbed exposure or natural sunlight-induced sunburn or tan on the back (test area) acquired within the four weeks prior to recruitment

8. Immunosuppression due to medications (such as organ transplant recipient) or disease (including HIV or haematological malignancy)
9. History of skin cancer, not including Basal Cell Carcinoma (BCC)
10. History of malignancy not curatively treated at least five years before screening visit with exception of BCC or cervical carcinoma in situ which may have been curatively treated within one year.
11. History of current use of illegal or 'recreational' drugs
12. Any condition which, in the opinion of the investigator, might put the subject at risk by participating in this study

Individuals will not be enrolled to the trial/study if they are participating in the clinical phase of another interventional trial/study or have done so within the previous 90 days. Individuals who are participating in the follow-up phase of another interventional trial/study, or who are enrolled in an observational study, can be co-enrolled where the CIs of each study agree that it is appropriate.

7. TRIAL PROCEDURES

The study will consist of the following interventions and assessments:

- Visit 1
    - Screening/inclusion & exclusion/informed consent
- Visit 2 (Day 0) Up to 30 days from Visit 1
    - Non-invasive reflectance measurement of the back for an objective measurement of skin colour.
    - Back irradiated with the LED-based phototest device at various wavelengths and doses
    - Back irradiated with an irradiation monochromator, which is our routine clinical phototest equipment, at various wavelengths and doses
    - Visual observation of the test sites for urticaria, for up to 30 minutes.
- Visit 3 (Day 1) +1 day from Day 0
    - Visual observation of MED on skin @ around 24 hours post initial exposure. Recording of skin response.
    - Further irradiation of the back with the LED-based phototest device. Doses delivered will be between the MED and the highest No-Response Dose (NRD).
    - Further irradiation of the back with the irradiation monochromator. Doses delivered will be between the MED and the highest No-Response Dose (NRD).

  - Non-invasive reflectance measurement may be taken to assess any non-visual changes.
  - If no MED following Day 0 irradiation then higher doses may be delivered.
- Visit 4 +1 (Day 2) day from Day 1
  - Visual observation of MED on skin @ around 24 hours post Day 1 exposure. Recording of skin response.
  - Non-invasive reflectance measurement may be taken to assess any non-visual changes.
  - If no MED following Day 1 irradiation, then further irradiation of the back may occur with the LED-based phototest device and/or irradiation monochromator at higher doses than delivered on Day 1.
- Visit 5 (Day 3), if required, +1 day from Day 2
  - Visual observation of MED on skin @ around 24 hours post Day 2 exposure. Recording of skin response.
  - Non-invasive reflectance measurement may be taken to assess any non-visual changes.

7.1. Recruitment

If the study criteria are met, the prospective participant will be offered the option of being recruited to the study and will be provided with the consent form and given opportunity to have any remaining questions about the study answered. Staff taking informed consent will be fully trained in Good Clinical Practice (GCP). After the participant has completed, signed and dated the consent form, the research team will schedule the study visits with the participant. The first intervention will take place within 30 days after the screening visit (visit 2).

Any participants not completing the interventional part of the study would be replaced in order to ensure that we obtain 50 full datasets (40 Fitzpatrick Skin Type I – III and 10 Fitzpatrick Skin Type IV – VI).

7.1.1. Participant identification

Recruitment to the study will be through several approaches. The study will be advertised via word of mouth and by an email advertisement circulated through the School of Medicine (University of Dundee) and NHS Tayside distribution list. It will also be advertised on social media and volunteers will be invited through the The Scottish Health Research Register and Biobank (SHARE) processses.

Interested individuals, who provide contact details by email or via SHARE, will then be contacted by telephone and provided with more detail about the study. If individuals continue to be interested, they will be asked a few eligibility, pre-screening questions during the telephone call and will be sent a participant information sheet. They will be given the opportunity to contact the department by telephone to opt in after they have had the opportunity to consider the participant information sheet. We will also ask if the potential participant is happy to be phoned or emailed on one occasion to follow-up on whether they wish to participate or not.

All potential participants will be given at least 24 hours to review the PIS and have the opportunity to discuss the study and have any questions answered before deciding if they wish to participate in the study. If willing to proceed, participants will be invited for a screening appointment (Visit 1). The participant will be required to provide identification to confirm identity at Visit 1.

If the participant is agreeable, written informed consent will be obtained by a Dermatologist or a delegated suitably qualified member of the research team. They will then undergo a series of screening questions and review of the skin on their back to ensure space for testing.

Staff directly involved in the study will be excluded from participating.

7.1.2. Screening

Potential participants will be initially pre-screened via phone call prior to progressing to the screening visit at the Photobiology Unit. At this visit written informed consent will be obtained prior to a screening questionnaire and review of the skin on the back.

7.1.3. Payment

Payments will be made to participants to compensate them for their time given to study. Payment follows guidance from the NIHR on costing public involvement in research (https://www.nihr.ac.uk/documents/payment-guidance-for-researchers-and-professionals/27392#payment-rates). Participants will be notified that these payments may be above the weekly limit for certain benefits and will be advised to speak to the Benefits Advice Service if required (https://www.citizensadvice.org.uk/scotland/about-us/contact-us/contact-us/contact-us/). Payments detailed below are incremental and are pro-rata equivalent to £150 per day.

- Withdrawal at any point prior to Visit 2 = £0
- Visit 2
    - Withdrawal after initiating study procedures on Day 0 but prior to completion of Day 0 = £65
- Visit 3 = £65

- Visit 4 = £50
- Visit 5 *if required* = £10
- Completion of all study procedures = £180 (£190 if Visit 5 required)

7.2. Consent

Written informed consent will be obtained from participants by a GCP trained member of the research team, recorded in the Delegation Log. This will take place in the Photobiology Unit prior to any study-related activity. Where a participant requests to speak with a physician from the study team the consent process will not be completed until the participant has spoken to the physician and has had all their questions answered to their satisfaction.

For adults who lose capacity during the study, their previous wishes will remain legally binding and this will remain valid unless the protocol changes significantly. Where appropriate the participant will be withdrawn from any further clinical intervention and agreement will be sought from a carer to allow data collection.

The informed consent process will be conducted in compliance with Sponsor's SOPs

7.3. Randomisation

There is no randomisation required for this pilot study.

7.4. Blinding

There is no blinding of participants or investigators required for this pilot study.

7.5. Emergency Unblinding

Not applicable

7.6. Baseline Data

Baseline data relating to the screening criteria for eligibility will be assessed and documented as per Baseline Clinical Assessment below.

7.7. Trial Assessments

All staff undertaking study assessments will be trained under the supervision of the CI.

Study assessments will be performed according to the Study Matrix in the appendices (Appendix: Study Matrix). Where study assessments identify any incidental findings, the participant will be informed and with their consent this information would be communicated to the participant's GP.

Baseline Clinical Assessment

A history and limited skin examination will be performed at screening to exclude participants with co-morbidities, medications or other clinical disorders that would constitute an exclusion from the study based on the eligibility criteria.

Reflectance Measurement

Non-invasive reflective measurement – A Konica Minolta CM-700d spectrophotometer will be used to take non-invasive reflectance measurements. The spectrophotometer provides numerical values related to the colour space defined by the International Commission on Illumination (CIE) in 1976, known as CIELAB. Three values are provided - L* (lightness), a* (red/green) and b* (blue/yellow). This is a numerical description of human colour vision and is a tool used in dermatology research for defining skin colour [Dadzie *et al.* 2022; Del Bino and Bernerd 2013].

Observations and Scoring

Visual score – The irradiated area will be visually assessed for erythema and other changes to skin appearance by trained photobiology clinical technologists. The irradiated area will be given a numerical and alphabetical score based on this visual assessment as per the Photobiology Unit standard reporting procedures shown in the following table:

Observation	Score
No evidence of any reaction	0
Faint but definite erythema filling the majority of the test site	1
Definite, marked erythema	2
Erythema with evidence of oedema	3
Erythema, oedema and blistering	4
Query results, i.e. uncertain result	?
Brown pigmentation	B
Flare	F
Petechia	G
Urticaria	U

Photographs

Photographs of the exposure areas will be taken on an as-required basis. Written consent for photographs will be sought at the initial screening visit. Photographs will be acquired on NHS Tayside authorised devices only and anonymised images stored as per this protocol's data management processes.

7.8. Long term follow-up assessments

Not applicable

7.9. Qualitative assessments

Not applicable

7.10. Withdrawal procedure

A participant is not obliged to give reason(s) for withdrawing prematurely and can withdraw at any point during the study for any reason. The CI will make a **reasonable** effort to ascertain the reason(s) for withdrawal while fully respecting the individual's rights. Those who withdraw will be identified and a descriptive analysis of them provided, including the reasons for their loss and its relationship to treatment and outcome.

If a withdrawal is due to an AE, it will be recorded on the CRF and AE log. All participants will be asked about any adverse events at each visit and these will be recorded in the trial AE log.

Participants are free to withdraw from the trial at any time. The reason, if known, will be recorded in the CRF.

Study data obtained prior to the point of participant withdrawal will be retained and analysed, as long as consent is still in place.

7.11. Storage and analysis of clinical samples

Not applicable.

7.12. End of trial

The end of the trial will be the final data collection timepoint for the final participant.

8. INTERVENTION

Participants will be exposed to UVB, UVA and visible wavelengths during this study.

These wavelengths will be delivered using LEDs from a LED-based phototest device, developed in-house by the Photobiology Unit at Ninewells Hospital. The area of skin illuminated per exposure is a circular area of 8 mm diameter. The device has been approved for electrical and mechanical safety by the Medical Physics department at Ninewells Hospital Dundee. The device has been fully characterised for its emission by the Photophysics Laboratory at the Photobiology Unit. The Photobiology Unit has extensive experience in dosimetry of optical radiation and performs measurements with traceability to national standards. The quality of dosimetry in the Photobiology Unit is recognised through UKAS accreditation to ISO17025 for the calibration of UV detectors. This is a medical device that does not require MHRA approval at this stage as it is made in-house and will be tested only in NHS Tayside without any commercialization purposes (Appendix: Notification to

MHRA Devices Flowchart). The Photobiology Unit have developed a Technical File as per good practice (Appendix: Technical File for LED Phototest Device). As a comparator, participants will also be exposed to UVB, UVA and visible wavelengths using an irradiation monochromator, which is the device used in routine clinical practice within the Photobiology Unit.

Study:

- Visit 2 (Day 0)
    - Multiple areas of the back will be exposed to UVB, UVA or visible wavelengths at multiple doses from both the LED-based device and the irradiation monochromator.
    - The central wavelengths of the LED-based device (plus wavebands at ± Full-Width Half Maximum) will be
        1. 300 nm (±15 nm)
        2. 340 nm (±11 nm)
        3. 365 nm (±9 nm)
        4. 385 nm (±12 nm)
        5. 415 nm (±14 nm)
        6. 455 nm (±14 nm)
    - The central wavelengths of the irradiation monochromator (plus wavebands at ± Full-Width Half Maximum) will be
        1. 305 nm (±7 nm)
        2. 335 nm (±27 nm)
        3. 365 nm (±27 nm)
        4. 400 nm (±27 nm)
        5. 430 nm (±27 nm)
    - The initial doses delivered will be based upon published literature and, if needed, will be updated based on experience with the first participants [Moseley *et al.* 2009]. Irradiations are expected to take up to 2 hours, with each exposure a maximum of 30 minutes.
- Visit 3 (Day 1)
    - Further irradiation of the skin on the back will take place to more accurately determine the individual's MED by irradiating at multiple doses. The doses shall be chosen such that they fall between the perceptible erythema and no response resulting from irradiation on Visit 2 as observed on Visit 3.
        - If no erythema is observed on Visit 3, then irradiation doses shall be chosen to exceed the delivered doses on Visit 2. The highest exposure doses will be limited to an exposure time of 30 minutes

- Visit 4 (Day 2)
    - If no erythema was observed on Visit 3, but is observed on Visit 4, further irradiation of the skin on the back will take place to more accurately determine the individual's MED by irradiating at multiple doses. The doses shall be chosen such that they fall between the perceptible erythema and no response resulting from irradiation on Visit 3 as observed on Visit 4.
        - If no erythema is observed on Visit 4, then irradiation doses shall be chosen to exceed the delivered doses on Visit 3. The highest exposure doses will be limited to an exposure time of 30 minutes

8.1. Concomitant medication

The study population will be healthy volunteers. The Principal Investigator (PI) must be consulted if any treatment is necessary for an acute medical condition. In this case, the PI or research nurse must record the medication administered in the subject's case report form (CRF). The PI and study medical monitor will decide whether the subject can continue with the study. Participants will only be included in the study if they are not taking any photosensitising medication or supplements at the discretion of the PI based on their clinical judgement.

9. PHARMACOVIGILANCE

9.1. Definitions

Adverse Event (AE)	Any untoward medical occurrence in a clinical research participant which does not necessarily have a causal relationship with study participation
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life threatening • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • Or is otherwise considered serious

9.2. Recording and Reporting Adverse Events

Participants will be asked at each visit to provide details of any adverse events, in particular relating to any study procedure.

All AEs and/or SAEs will be recorded on the AE Log in the CRF and will be assessed for severity by the CI or delegate. AEs/SAEs will be recorded from the time a participant consents to join the study until the participant's last study visit.

The CI will make a clinical judgment as to whether or not an AE is of sufficient severity to require the participant's removal from the study. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant should, if required, be offered an end of study assessment and be given appropriate care under

medical supervision until symptoms cease, or the condition becomes stable. SAEs will be followed up until 30 days after participant's last visit.

The CI or delegate will ask about the occurrence of SAEs and hospitalisations at every visit during the study. **SAEs which are both unexpected and related to study participation** will be submitted on an HRA NCTIMP Safety Report form to the REC by the CI, within 15 days of becoming aware of the SAE, and copied to the Sponsor Research Governance Office.

Pre-specified outcome(s) will not be classed as an AE but as an outcome. Elective admissions and hospitalisations for treatment planned prior to randomisation, where appropriate, will not be considered as an AE. However, AEs/SAEs occurring during such hospitalisations will be recorded.

Premature termination of the trial may occur in the event of any unexpected severe local (eg. skin blistering) or systemic reactions as assessed by the CI.

10. STATISTICS AND DATA ANALYSIS

10.1. Sample size calculation

This is a pilot study to investigate the feasibility of the LED-based phototest device for exposure of the skin.

The sample size of 50 subjects is selected on the basis of practicality and our experience of determining reference intervals for phototesting in the past. Most importantly, we will derive appropriate confidence intervals around our reference ranges, and so take into account variability when we are extrapolating findings from our study sample to the wider population.

10.2. Planned recruitment rate

The recruitment period is expected to be 9 months.

10.3. Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be developed and finalized prior to analysis. We will find the 95% reference interval (that is, the 2.5th and the 97.5th percentile) for MED for each waveband. We will derive, through boot strapping, the 99% confidence interval around this reference interval. In practice, when using the findings from the study in determining whether or not results of patients attending for testing are likely to be 'normal' or not, the important value will be the lower end of the 99% confidence interval of the 25th percentile.

10.4. Interim analysis and criteria for the premature termination of the trial

Not applicable.

10.5. Participant population

All patients which have been exposed to at least one dose from the LED phototest device will be analysed on an Intention-to-treat (ITT) basis.

10.6. Procedure to account for missing or spurious data

As the trial duration is short, missing data are not expected. Where patients withdraw from treatment early, data up to the timepoint of withdrawal will be used in the analysis. No replacement strategies for missing or incomplete data will be performed

11. DATA MANAGEMENT

11.1. Data collection tools and source document identification

Delegated research staff will enter the data required by the protocol into the CRFs following training in the definitions and methods used in completing the CRF. The CRFs will act as source data.

11.2. Data handling and record keeping

Data management will be conducted in compliance with Sponsor's SOPs on Data Management.

The data management system (DMS) will be Excel, as approved by Sponsor.

The DMS will be based on the protocol and paper CRF for the trial/study and individual requirements of the investigators. The CRF will collect only information that is required to meet the aims of the trial/study and to ensure the eligibility and safety of the participant. The trial/study database will be compliant with Sponsor's SOPs.

The database is managed in line with all applicable principles of medical confidentiality and data laws. The Data Controller will be the University of Dundee and the Data Custodian will be CI.

The CI may delegate CRF completion but is responsible for completeness, plausibility and consistency of the CRF. Any queries will be resolved by the CI or delegated member of the trial/study team.

Database lock will be conducted in compliance with Sponsor's SOPs.

11.3. Access to data

Hardcopies of CRF will be stored in a study file in a secure office, with identifiable documents stored in a separate file and office. The DMS will be stored on QPulse (Quality Management System software) and access restricted to appropriate members of the research team. QPulse is software

held on an NHS Tayside server, with documentation embedded and held on the same server. This is subject to NHS Tayside's Information Governance and Information Security policies.

11.4. Archiving

Following completion of the study, the site file will be stored in a locked cupboard within the Photobiology Unit, Ninewells Hospital, for a period of 5 years. The key to the cupboard will be kept in a locked filing cabinet under the oversight of the CI. The anonymised DMS will be stored on QPulse for a minimum of 5 years.

12. MONITORING, AUDIT AND INSPECTION

The CI, PI and all institutions involved in the study will permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Research Ethics Committee (REC) review and reports

The study will be conducted in accordance with the principles of good clinical practice (GCP).

In addition to Sponsorship approval, a favorable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the study.

Sponsor SOP will be followed for any amendments after original approvals from all relevant review bodies. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial (note that amendments may also need to be reviewed and accepted by NHS R&D departments before they can be implemented in practice at site).

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended

It is the Chief Investigator's responsibility to produce the annual reports as required.

The Chief Investigator will notify the REC of the end of the trial. If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC

13.2. Peer review

This project has been peer-reviewed by the funder, the British Skin Foundation.

13.3. Public and patient involvement

This study has been discussed with, and Participant Information Sheets (PIS) reviewed by, the Tayside Public and Patient Involvement (PPI) Group. The comments from this group have been invaluable in informing the content of the protocol and PIS.

13.4. Regulatory compliance

Before enrolling patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment.

13.5. Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms (see Sponsor SOP on reporting breaches) and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

13.6. Notification of serious breaches to GCP and/or the protocol

All breaches of GCP and protocol will be reported to the sponsor without delay in line with Sponsor's SOPs.

13.7. Data protection and patient confidentiality

The CI and trial staff will comply with all applicable medical confidentiality and data protection principles and laws with regard to the collection, storage, processing and disclosure of personal data.

The CI and trial staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or equivalent.

All trial records and personal data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate trial staff only. Computers used to collate personal data will have limited access measures via user names and passwords.

Personal data concerning health will not be released except as necessary for research purposes including monitoring and auditing by the Sponsor, its designee or regulatory authorities providing that suitable and specific measures to safeguard the rights and interests of participants are in place.

The CI and trial staff will not disclose or use for any purpose other than performance of the trial, any personal data, record, or other unpublished, confidential information disclosed by those individuals for the purpose of the trial. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated personal data relating to participants will be restricted to the CI and appropriate delegated trial staff.

Where personal data requires to be transferred, an appropriate Data Transfer Agreement will be put in place.

Published results will not contain any personal data that could allow identification of individual participants.

13.8. Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

There are no competing interests that might influence trial design, conduct or reporting.

13.9. Insurance and Indemnity

The University of Dundee is Sponsoring the study in Scotland.

Insurance – The University of Dundee holds Clinical Trials indemnity cover which covers the University's legal liability for harm caused to participants..

Where the study involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the Clinical Negligence and Other Risks Insurance Scheme ("CNORIS"). Tayside Health Board will maintain its membership of the CNORIS which covers the legal liability of Tayside in relation to the study.

Indemnity – The Sponsor does not provide study participants with indemnity in relation to participation in the Study but have insurance for legal liability as described above.

13.10. Amendments

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office(s) as required. Amendments to the protocol or other study docs will not be implemented without these approvals.

13.11. Post-trial care

This is a study of healthy volunteers. No further care will be provided by the study team once participants have completed the study.

13.12. Access to the trial dataset

As this is a preliminary study on a specific device there are no current plans to make the dataset available to other investigators. The CI and study team in Tayside will have full access to the anonymised dataset.

14. DISSEMINATION POLICY

14.1. Dissemination policy

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. Publications will be reviewed according to the agreed contractual terms of the grant funding but will not restrict the general rights outlined above for investigators to publish the results of the study.

14.2. Authorship eligibility guidelines and any intended use of professional writers

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared for presentation and publication in peer-reviewed journals

15. REFERENCES

del Bino, S., & Bernerd, F. (2013). Variations in skin colour and the biological consequences of ultraviolet radiation exposure. *British Journal of Dermatology*, *169*(SUPPL. 3), 33–40. https://doi.org/10.1111/BJD.12529

Dadzie, O. E., Sturm, R. A., Fajuyigbe, D., Petit, A., & Jablonski, N. G. (2022). The Eumelanin Human Skin Colour Scale: a proof-of-concept study. *British Journal of Dermatology*, *187*(1), 99–104. https://doi.org/10.1111/BJD.21277

Moseley, H., Naasan, H., Dawe, R. S., Woods, J., & Ferguson, J. (2009). Population reference intervals for minimal erythemal doses in monochromator phototesting. *Photodermatology, Photoimmunology & Photomedicine*, *25*(1), 8–11. https://doi.org/10.1111/j.1600-0781.2009.00391.x

Appendix: Study Matrix

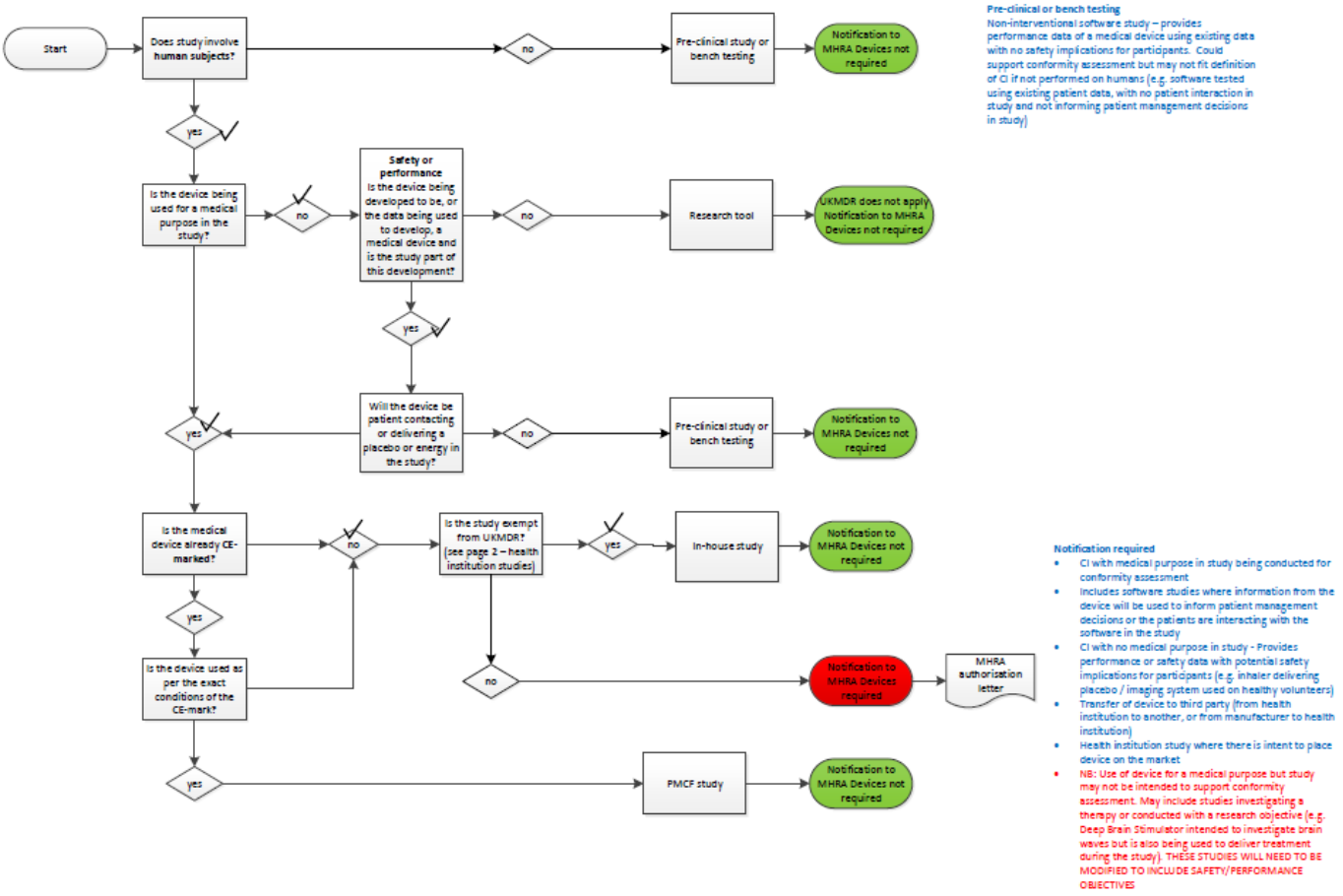
	Visit 1	Visit 2 (<=+30 days)	Visit 3 (+1 day)	Visit 4 (+1 day)	Visit 5 *if required* (+1 day)
Type of Visit	Hospital - Screening	Hospital	Hospital	Hospital	Hospital
Timeline	Up to 30 days	Day 0	Day 1	Day 2	Day 3
Eligibility	x				
Informed Consent	x				
Inclusion/exclusion	x				
Medical History	x				
Con Meds	x	x	x	x	x
Physical Examination	x				
Photographs		x	x	x	x
Reflectance measurement		x	x	x	x
LED Irradiation		x	x	x (if required)	
Irradiation monochromator		x	x	X (if required)	
Up to 30-minute post exposure observation & scoring		x	x	x (if required)	
24-hour (± 3 hours) observation & scoring			x	x	x
Record Adverse Events		x	x	x	x

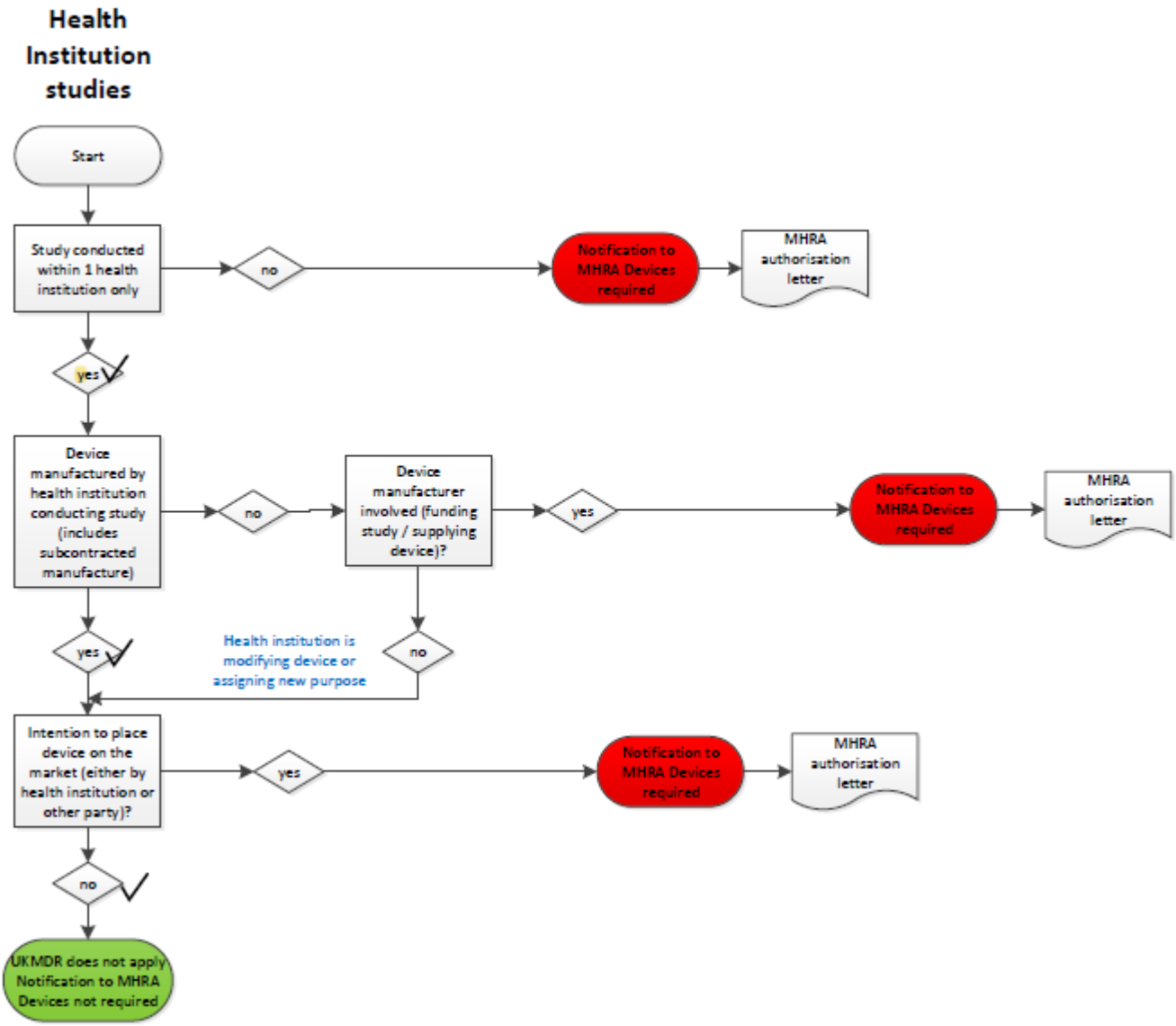
Appendix: Technical File for LED Phototest Device

See attached documents.

Appendix: Notification to MHRA Devices Flowchart

MHRA Flowchart indicating that the UK Medical Device Regulation does not apply and Notification to MHRA Devices is not required.




Health Institution studies
Start
Study conducted within 1 health institution only
no
Notification to MHRA Devices required
MHRA authorisation letter
yes
Device manufactured by health institution conducting study (includes subcontracted manufacture)
no
Device manufacturer involved (funding study / supplying device)?
yes
Notification to MHRA Devices required
MHRA authorisation letter
yes
Health institution is modifying device or assigning new purpose
no
Intention to place device on the market (either by health institution or other party)?
yes
Notification to MHRA Devices required
MHRA authorisation letter
no
UKMDR does not apply Notification to MHRA Devices not required

Appendix: Summary of Skin Type Categories

Skin Type	Typical features	Typical reactions to solar radiation
I	Pale white skin, blue/green eyes, blond/red hair	Always burns easily and severely (painful burn); doesn't tan
II	Fair skin, blue eyes	Usually burns easily and severely (painful burn); tans minimally or lightly
III	Darker white skin	Burns moderately and tans about average
IV	Light brown skin	Burns minimally, tans easily, and above average with each exposure; exhibits immediate pigment darkening (IPD) reaction
V	Brown skin	Rarely burns, tans darkly and easily
VI	Dark brown or black skin	Never burns, always tans darkly

Based on the first 45–60 min (≅ 2–3 MED) exposure to the summer sun (early June) at sea level.

References:

Fitzpatrick T.R. *The validity and practicality of sun-reactive skin types I through IV* Archives of Dermatology 1988; 124: 869-871.

Oakley, A. Fitzpatrick skin phototype. DermNet. https://dermnetnz.org/topics/skin-phototype (Last accessed 13.07.2023)