Study Title: A physiological study to optimise a novel low-level light treatment for digital ischaemia in patients with systemic sclerosis

Short Title: Light treatment for scleroderma finger ulcers - study 2

Study Protocol

IRAS ID: 351238

R&I Ref: 24MSK13-S

Protocol version and date: V4.0; dated 26/02/2025

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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 investigation without the prior written consent of the Sponsor

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

For and on behalf of the Study Sponsor:

Signature:

Name (please print): Hannah Howlett Date: 27/02/2025

Position: Deputy Research and Innovation Manager

Chief Investigator:

Signature:

Name (please print): Michael Hughes Date: 27/02/2025

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KEY STUDY CONTACTS

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Funder(s)	No grant funding – Dr Michael Hughes - PI account
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ROLE OF STUDY SPONSOR

Northern Care Alliance NHS Foundation Trust assumes overall responsibility for the initiation and management of the study. The sponsor has delegated responsibility to the Chief Investigator for study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES

Trial Management Group to oversee proceedings.

Dr Michael Hughes - Consultant Rheumatologist and Chief Investigator

Dr Graham Dinsdale - Clinical Scientist

Ms Joanne Manning - Senior Vascular Technician

Mr Paul New - Study Co-ordinator)

Ms Hannah Howlett - Deputy Research and Innovation Manager

Patient & Public Involvement Group

To recruit 2 patients from Salford Royal Hospital with systemic sclerosis (SSc), to provide feedback on patient facing documents and relevance of study to patients with SSc.

1 Study Summary

Study Title	A physiological study to optimise a novel low-level light treatment for digital ischaemia in patients with systemic sclerosis
R&I Reference	24MSK13-S
Research Question/Aim(s)	**Primary Aim:** To assess the safety, tolerability, and efficacy (as assessed by surrogate measurement of skin perfusion and temperature) of our low-level light therapy (combined red, infrared and violet wavelength). concerning dose finding with lower and higher irradiances, including evidence of a biphasic response with higher irradiance dose. **Secondary Aim:** To investigate potential SSc patient- and disease-related factors relevant to cutaneous irradiation with low-level light therapy (LTTT). • Age and disease duration. • Skin thickness.
Study Participants	Patients with SSc
Planned Size of Sample	20
Planned Study Period	Study start date: 14/02/2025 Recruitment end date: 13/02/2026 Final study end date: 20/02/2026

2 Lay Summary

Digital (finger) ulcers are common in patients with systemic sclerosis (SSc) otherwise known as scleroderma and many of the current treatments used can cause side effects or are not effective. We want to investigate a novel light-based therapy to potentially treat digital ischaemia (low blood flow) that causes digital ulcers.

In our previous study, our custom-built light-based treatment device, consisting of red, infrared, and violet wavelengths was found to be safe and feasible. There were also some early signals of potential benefit for digital ulcers in patients with SSc. To take this treatment approach forward, we now need to refine the optimal 'dose' of light.

Participants wishing to take part will need to attend Salford Royal Hospital for three study visits. At the first visit the research team we will examine the participant's fingers and back of their hands for any skin thickness changes (gently pinching the skin) as is routinely performed in the scleroderma outpatient clinic. Skin thickness will also be measured at these sites using an ultrasound machine.

At each visit, participants will receive one of three randomised 'doses' of the combination light therapy. The research team wishes to understand how the skin (blood flow and temperature) reacts to increasing dose of light. All patients will receive the three 'doses' of light over the three study visits (but not all in the same order), there is no placebo treatment. The light application to the skin will take approximately 15 minutes to complete.

We will measure the blood flow and temperature of the skin immediately before, directly after, and then every 10 minutes for 90 minutes after the light therapy. These will be measured using a type of scanner called 'laser Doppler imaging' and a thermal camera, which will each take approximately 1 minute (or less) per scan.

3 Background

Systemic sclerosis (SSc) is a complex autoimmune connective tissue disease characterised by microvascular abnormalities, fibrosis of the skin and internal organs, and immune system activation [1]. Digital ulcers (DUs) are common in patients with SSc and are responsible for much of the pain and disability associated with the disease [2,3].

SSc-Digital Ulcers (DUs)

Half of patients with SSc report a history of DUs, often occurring early in the course of the disease [4]. DUs, in particular those located on the fingertip, are believed to be ischemic in aetiology [5]. Patients with SSc also commonly have marked finger contractures, which may predispose to recurrent trauma and can make wound care challenging for patients [6].

Despite there being systemic (pharmacological) therapies available to prevent and treat intercurrent DUs [7], recurrent ulceration remains a major source of morbidity in some patients with SSc [8,9]. Furthermore, DUs are often superficially infected, in particular, with Staphylococcus aureus [10], and can undergo deeper bony progression. Unfortunately, despite targeted intervention, in some patients, digital amputation may be necessary for refractory DUs.

There are limited data concerning the local (wound) management (non-surgical and surgical) for SSc-DU [11–13]. However, there is strong expert opinion favouring the local treatment for SSc-DU, which would likely be better tolerated by patients (e.g., through the absence of significant vasodilatory side effects from systemic therapies) and could potentially be administered in the community (e.g., avoiding the cost, and inconvenience to patients themselves, associated with the need for hospitalisation). To this end, a number of other local

approaches to DU treatment have been suggested to have potential benefit [11–13]. However, the current evidence in SSc is still very limited and does not strongly support any specific local treatment.

Low-level light treatment for cutaneous ulceration

Low-level light therapy (LLLT) is an area of growing clinical interest. While its use has been largely empirical and complicated by the application of various wavelengths and dosimetric parameters, it is now reported in a number of studies (albeit with a lack of any high-quality randomised controlled trials) to be a safe and effective treatment for refractory skin (diabetic, pressure, and venous) ulcers [14]. In summary, the majority of previous studies have reported that LLLT was associated with around an additional 50% (range of 30–60%) in improvement in ulcer status compared with the comparator group (conventional wound care and/or placebo light treatment) [14–24].

Light treatment within the red and near-infrared spectrum is believed to stimulate a wide number of cellular processes (often referred to as ‘biostimulation’) which are thought to benefit wound healing, including (but not limited to) stimulation of fibroblast and macrophage number and function, increasing leucocyte mobility, modulation of growth factors and inflammatory mediators, and by promoting collagen deposition and neovascularisation [25,26].

Infrared light is also associated with ambient heating and an increase in blood flow (although this is likely short-lived), and improved tissue oxygenation. Red light can also have an antimicrobial effect through excitation of naturally occurring porphyrins (30). In a blinded, randomised, placebo-controlled, single treatment trial, photodynamic therapy with red light and an exogenous photosensitiser caused a significant reduction in bacterial load of diabetic ulcers, and a trend toward ulcer healing [27].

Violet light also has an antibacterial effect including activity in vitro against Staphylococcus aureus [28]. Impact of the LLLT may occur both via effects on the ulcer bed and on the ulcer margins, including with respect to bacteria present. While blue light can reach bacteria residing on the surface or within the epidermis, bacteria can also colonize deeper dermal components of the skin, and blue light will be less effective than red/infrared in reaching these. DUs in patients with SSc are relatively superficial, with an average depth of 1 mm (as measured by high-frequency ultrasound); therefore, this is unlikely to be an important disadvantage [29]. While there is much less of a precedent for the use of violet (or blue) light to treat ulcers, it is important to consider that blue light is more photochemically active than red light and causes more reactive oxygen species generation [30]. Blue light has been shown to increase perfusion through stimulation of local nitric oxide (NO) release, with relaxation of vascular smooth muscle, and to increase wound healing in a skin excision model [31].

LLLT for SSc-DUs

We have previously developed at Salford Royal Hospital a custom-built LLLT device comprising infrared (850 nm), red (660 nm), and violet (405 nm) LEDs was utilized (Figure 1).

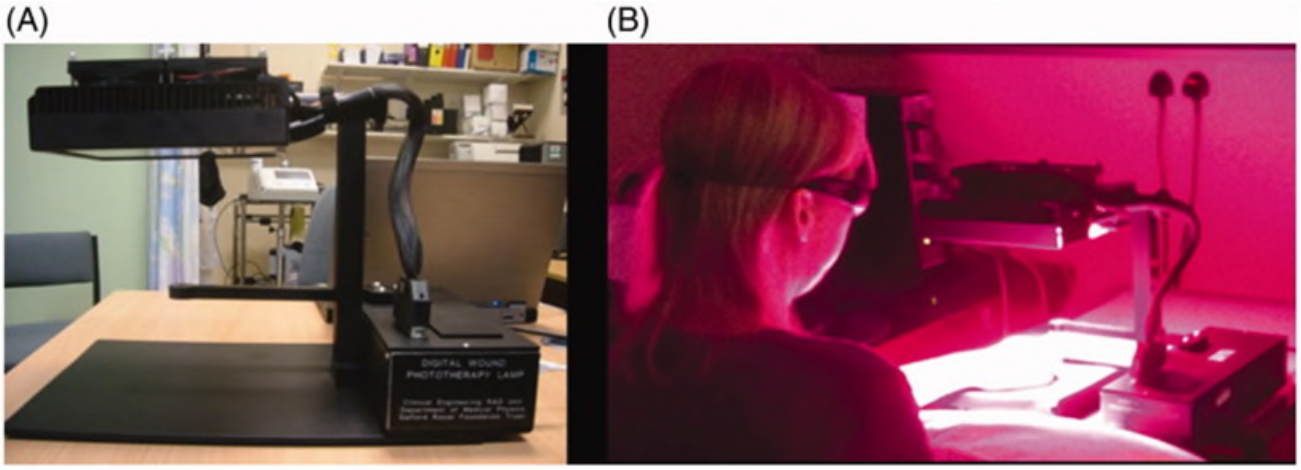

Figure 1. LLLT for SSc-related DUs. A: Side profile of the light device. B: The light device in operation treating an extensor aspect DU in a patient with SSc. The distance from the panel of LEDs to the treatment area is approximately 15 cm.

Unlike previous studies, all three specifically chosen wavelengths were given simultaneously. SSc-DUs were irradiated with 10 J/cm^2 twice weekly for 3 weeks, with follow-up at weeks 4 and 8 [32]. Any safety concerns were documented. Patient opinion on time to deliver, feasibility, and pain visual analogue score (VAS; 0-100, 100 most severe) was collected. Patient and clinician DU global assessment visual analogue score (VAS) were documented. DUs were evaluated by laser Doppler perfusion imaging pre- and post-irradiation. In all, 14 DUs in eight patients received a total of 46 light exposures, with no safety concerns. All patients considered LTTT 'took just the right amount of time' and was 'feasible', with a low associated mean pain VAS of 1.6 (SD: 5.2). Patient and clinician global DC VAS improved during the study (mean change: -7.1 and -5.2, respectively, both p <0.001). DU perfusion significantly increased post-irradiation.

Recently, Spinella et al [33], report their positive preliminary evaluation of the role and effectiveness of blue light photobiomodulation therapy with EmoLED® for scleroderma skin ulcers (SU). The authors retrospectively analysed 12 consecutive patients with a total of 15 SU on finger hands. All patients were treated with adequate systemic therapy and local treatment for SU; after a standard skin ulcer bed preparation with debridement of all lesions, EmoLED® was performed. All patients were locally treated every week during 2 months of follow-up; and SU data were collected after 4 weeks (T4) and 8 weeks (T8). Eight SSc patients with comparable SU were also evaluated as controls. The application of EmoLED® in addition to debridement apparently produced faster healing of SU. Complete healing of SU was recorded in 41.6% cases during EmoLED® treatment. Significant improvements in SU area, length, and width, wound bed, and related pain were observed in EmoLED® patients from T0 to T8. Control subjects treated with standard systemic/local therapies merely showed an amelioration of SU area and width at the end of the follow-up. No procedural or post-procedural adverse events were reported.

Rationale for further development of our novel LLLT for SSc-DU

Our previous feasibility study demonstrated that our novel LTTT for DUs was safe, feasible, and well tolerated. Furthermore, there was an early tentative suggestion of treatment efficacy. There is a significant therapeutic rationale to develop locally acting treatments for SSc-DU, which likely would be better tolerated by patients, and could be administered potentially in the community (our outpatient setting under medical supervision), thereby avoiding the costs and inconvenience from inpatient hospitalisation. Furthermore, many previous studies have found comparable efficacy at lower doses (total dose 5 to 10 J/cm^2). Although, some studies have also found positive results with much higher doses, such as 20J/cm², 70J/cm², or even higher.

However, a biphasic response to light is well known, and therefore there is a need to scientifically determine the dose-ranging of LLLT for SSc-DU, including examination of potential patient- and disease-related factors.

4 Objectives

Primary Objective: To assess the safety, tolerability, and efficacy (as assessed by surrogate measurement of skin perfusion and temperature) of our LLLT (combined red, infrared and violet wavelengths) concerning dose finding with lower and higher irradiances, including evidence of a biphasic response with higher irradiance dose.

Secondary Objective: To investigate potential SSc patient- and disease-related factors relevant to cutaneous irradiation with LTTT.

- Age and disease duration.
- Skin thickness.

5 Study Design

A physiological, clinical laboratory-based, study of LLLT.

LTTT experimental setup

A new LTTT device (Figure 2) shall be constructed in-house by Medical Physics at Salford Royal Hospital and subject to appropriate safety and quality assurance checks.

Allocation of LLLT intervention

Prior to the initial study visit, an independent member of the study team shall perform the randomisation procedure. Randomisation to be done in house by study team (e.g., using random number generator/excel). All patients shall receive combined sequential red (810nm)/infrared (850nm) followed by blue (410nm) wavelengths. The dose per visit shall be dose-escalated in a pre-determined randomised order over the course of the three study visits: 5 J/cm^2 or 10 J/cm^2 (i.e., the dose of our previously explored LLLT), and 20 J/cm^2

Figure 2. New LED experimental setup for our proposed laboratory-based study. Left: LED array (Hogga) to deliver red (660nm) and near-infrared (850nm) light – the same as utilised in our previous study. Right: LED device (Hogga) to deliver blue (415nm) light (very similar to our previous study – 405nm).

A custom-built configuration shall allow irradiation of the participants fingers/hands. The wavelengths shall be delivered sequentially to the patient's treated hand (i.e., red/infrared and then blue light). Similar to our previous study, we envisage that a future LTTT device would uniquely combine and deliver all three wavelengths simultaneously. However, for our planned experimental approach by using available LED-based light systems, this will enable us to achieve the intended aims of our study and is significantly less expensive than constructing a new custom-built treatment device.

Participation

Taking part is voluntary and it is up to patients to decide whether or not to take part. If they decide to take part, they are free to withdraw at any time without giving a reason. A decision to withdraw at any time will not affect their standard of any care they receive. If they do wish to withdraw, they simply need to inform a member of the research team and they will cancel any planned future visits. Any images and data collected up to the point of withdrawal will be retained by the research team for use in the study.

Participant will potentially be in the study for up to 7 days. If they lose capacity for any reason during that time they will be withdrawn from the study and no further study visits will take place. Any images or data collected before the participant in question lost capacity would be retained for use in the study analysis.

Study visit protocol

Participant progression throughout the study is presented in Figure 3. Study visits will be conducted in a temperature-controlled (at 23°C) laboratory at Salford Royal Hospital. Patients will attend a total of 3 study (morning) visits over 3 (ideally consecutive) days. The minimum time between study visits is 1 day, and the maximum time between study visits shall be 3 days. Patients can attend consecutive days because there is not expected to be any significant carry-over therapeutically relevant effect from the LLLT. Relevant patient- and disease-related demographics and characteristics shall be collected. At each study visit, any relevant change/s to current drug treatment will be documented.

Participants will not be paid to take part in the study; however, they will be reimbursed reasonable travelling expenses for each of their 3 study visits

Figure 3. Participant progression throughout the study. We assume no significant therapeutic carry over effect between the LLLT irradiation between study visits (minimum of 24 hours).

Preparation

Patients will be asked to abstain from caffeine-containing drinks and from smoking for at least 4 hours prior to study.

Clinical data

After signing the informed consent form, the patient will be interviewed by a member of the study team using a standard proforma and/or standardised proformas.

This will include:

- Demographic information.
- Gender.
- Age.
- Smoking status
- Fitzpatrick skin type/colour (for potential effects of melanin).
- Modified Rodnan skin score assessment
- Current medication/s.
- Past medical history.
- Disease-related history (e.g., history of severe digital vascular disease).
- Record of ulcers present and past and also of location, duration etc.
- Handedness (i.e., dominant hand).

Application of the LLLT device

We will apply the LLLT (for all study visits) to the dominant hand unless there are specific reasons not to, which will be documented. For example, due to patient preference or major musculoskeletal involvement with upper limb disability/contractures prohibiting correct positioning for the application of the LLLT.

Both the patient and device operator/s will wear appropriate safety goggles (as advised by Medical Physics at Salford Care Royal Hospital) at all times whilst the LLLT device is in operation. The patient will place their hand within the treatment area of the light-based device (total treatment area of approximately 15cm^2), aiming to centralise the hand (fingers/thumbs and dorsal aspect) within the treatment region. The device will be directly controlled by an attached custom-built computer interface. At each study visit, the device will undergo a period of automatic calibration before use.

Using the custom interface/s, the dose of the wavelengths can be selected to be delivered as prior study. The dose will be delivered either at 5 J/cm^2, 10 J/cm^2 or 20 J/cm^2 based upon the patient study visit sequence/randomisation. The LLLT will take approximately 10-15 minutes to complete.

Outcome measures

Assessment of safety and tolerability

At each treatment study visit any safety issues (between visits) will be documented (e.g., new concerns about cutaneous changes). This will be documented on a separate safety CRF at visits 2 and 3 (attached with this application). Patient reported pain on a VAS scale (0-100, where 100 is the most severe pain imaginable by

the patient) directly attributed to the LLLT will be recorded immediately after treatment, on a separate tolerability CRF at visits 1, 2 and 3 (attached with this application), to assess tolerability, at each study visit.

Assessment of efficacy

Laser Doppler imaging (LDI); LDI which measures blood flow allows a perfusion map (in arbitrary units) to be produced of the studied area. We will perform LDI immediately before and after the light exposures and then every 10 minutes for 90 minutes. LDI will include all the digits (thumb and four fingers) and dorsum of both the *treated* and *untreated* hands. Bilateral (matching) standard regions of interest (ROI) shall be assessed on the treated and untreated hands all LDI time points. The rationale of imaging these sites is to demonstrate an objective *localised* increase in skin perfusion with light treatment, and whether this differs between the digits and dorsum of the hand.

Thermography: Thermographic assessment measures skin temperature and provides an indirect measure of small and large blood vessel function and can also be applied to SSc-DUs. Standardised thermographic images shall be acquired immediately before and after the light exposures, and then every 10 minutes for 90 minutes. As for LDI, thermography will simultaneously image the whole treated hand to capture the fingers and dorsal aspect, and with contralateral counterparts on the untreated hand.

Assessment of persistent cutaneous digital ischaemia

Taken from the hand original acquired LDI and thermography images (as above), for any digital (finger) ulcers (DU) or pitting scars (DPS) present, perfusion measurements will be assessed at the lesion center (DU/DPS ‘core’) and immediately adjacent tissue (DU/DPS ‘periphery’).

Assessment of digital skin fibrosis:

Rodnan skin score: By a trained assessor using the modified Rodnan skin score by manual palpation (0-3 score, where 0 is normal and 3 is severe skin fibrosis/sclerosis).

High frequency ultrasound (HFUS): HFUS imaging (Episcan I-200, frequency 35 MHz) will be performed (using sterile ultrasound gel) along the visually apparent mid-point of the proximal and middle phalanges. From, this the HFUS images can be used to markup and extract measures of skin thickness (averaged per hand and individual proximal and middle phalanges).

6 Recruitment

Twenty patients > 18 years of age with SSc-spectrum disorders will be recruited. Patients with SSc will be prospectively recruited at Salford Royal Hospital either at their routine clinic attendance or through contacting patients who have previously given their permission to be contacted about future relevant studies.

6.1 Eligibility Criteria

Inclusion Criteria:

- Clinician confirmed diagnosis of SSc-spectrum disorder.
- Eighteen years of age or older at the time of recruitment.
- Able to give full informed consent.
- Steady dose (for at least two weeks) of relevant prescribed drug (e.g., vasodilatory and vasoactive) therapies for SSc-associated vasculopathy.

Exclusion Criteria:

- Patients receiving treatment with intravenous vasodilatory/vasoactive therapy (e.g., iloprost)
- Finger DUs currently requiring hospital admission (e.g., to receive iloprost) or awaiting surgery for digital vasculopathy.
- Currently receiving phototherapy for clinical reasons (e.g., ultraviolet-B therapy).
-

We will use a purposeful sampling to recruit patients with representative spectrum of SSc:

- Disease duration: 'early' (<5 years) and 'late' (>5 years).
- Limited vs. diffuse cutaneous disease/subsets.
- Severity of digital (finger) skin sclerosis (i.e., sclerodactyly) – although it is likely that many patients will have mild to moderate digital fibrosis.

6.2 Recruitment and Consent Procedure / Data collection procedure

Potential patients will be recruited from the specialist SSc clinic at Salford Royal Hospital. Primarily they will be identified as potential participants during the outpatient encounter. However they may also be identified through review of the patient electronic records and clinic lists by a member of the direct care team. They may also be approached during inpatient admissions at Salford Royal Hospital.

Potential patients will be given the patient information sheet and consent form. They will be given as much time as they require to read the documentation and to ask questions. Consent may be taken therefore when first approached. If they require further time to consider (e.g. beyond the day they attended the outpatient department), then they will be provided with the telephone numbers and email addresses of members of the direct care team to allow them the opportunity to ask any questions they may have. This will be followed up by a telephone call from one of the direct care team to ascertain whether or not they would be interested in taking part. This would be at least 24 hours after they received the study information (including patient information sheet and consent form) to allow time to consider their decision.

Members of the direct care team will also write to patients with a history of digital ulceration to offer them the opportunity to participate. This will include a covering patient invitation letter and the study patient information sheet. This will include the contact details of how to contact the research team if they wish to participate and/or have any queries. This will be followed up with a phone call (no less than 7 days after being sent) to follow up if they have not contacted the research team within this time period.

Informed consent will be taken by either a member of the direct care team or the research team. These will include the following individuals: Dr Michael Hughes, Dr Andrea Murray, Dr Graham Dinsdale, Mrs Joanne Manning and Mr Paul New, all of whom have substantive or honorary contracts with Northern Care Alliance NHS Foundation Trust (NCA) and up to date GCP training.

6.3 Equality

The NHS Constitution states that access to research should be available to all; however the evidence indicates that participation in health research does not reflect the demography of the local or national population. This may have an impact on the validity and reliability of research findings when applied to the general population. Improving equality and access to research is one of the Sponsor's organisational priorities..

6.4 Study Duration

The study will recruit for a I year period with a proposed start date of 14/02/2025 with a recruitment end date of 13/02/2026 and a study end date (last patient, last visit) of 20/02/2026. Patients will attend a total of 3 study (morning) visits over 3 (ideally consecutive) days. The minimum time between study visits is 1 day, and the maximum time between study visits shall be 3 days. The patient will therefore be in the study between 3 days and 7 days. Study visits will last approximately 2 hours. We will aim to complete study write up within 12 months of the study ending. The study end date will be defined as the last study visit of the last participant recruited.

6.5 Withdrawal Criteria

Participants will be allowed to withdraw from the study at any point. We will not collect any further data from this participant however will use data available during their time in the study for the final study analysis. If it is in the participant's best interest the clinician in charge of the study may also choose to withdraw the participant. If participants lose capacity for any reason during that course of the study, they will be withdrawn.

7. Data Management and Statistical Analysis

7.1 Data Management

- All outcome measures will be recorded on standardised case report forms and safety/tolerability questionnaires.
- All participant data collection documentation including consent forms, will all be stored in a secure area and will never be taken off site.
- The following demographic data will be collected for the purpose of this study. Participant's address and telephone number will be collected for recruitment purposes only, in order to contact them, to inform them about the study and to see if they wish to take part.
    - Gender
    - Age
    - Hospital number
    - Address
    - Telephone number
- Data will be transcribed from CRF / Questionnaires into excel spreadsheets / central database by members of the research team.
- The central electronic database will be pseudonymised, password protected and only accessible to certain members of the study team.

7.2 Statistical Analyses

To assess tolerability of irradiance wavelengths, VAS scores will be graphically explored. To observe the change over time, area under the curve will be calculated for each patient to estimate the blood flow/temperature, and a t-test will be used to test for differences. Our physiological study data shall inform the sample size calculation of a future feasibility RCT. However, in our previous investigation, which included eight patients (with 14 SSc-DU), we observed

an increase in perfusion of 15-32% post-irradiation with LTTT. We shall perform tentative analyses to explore the impact of our specified patient- and disease-related factors.

The study team including Dr Michael Hughes, Dr Graham Dinsdale, Ms Joanne Manning and Mr. Paul New, will be responsible for transcribing, coding, de-identifying, storing/transferring, accessing and archiving study data.

8 Regulatory and Ethical Considerations

8.1 Study Conduct

- The study will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and other applicable guidance.
- The study will not commence until all regulatory approvals are in place, which will include HRA Approval, REC Approval and confirmation from local R&I that the Trust has capacity and capability to carry out the research.
- All amendments will be submitted to HRA and/or REC by the sponsor and disseminated to sites as applicable.

8.2 Monitoring and Audit

- The study will be subject to the standard procedures for monitoring and auditing of studies by the sponsor.
- Any changes to the protocol will be agreed with the sponsor prior to submission to HRA and/or REC for review, with the exception of where urgent safety measures apply.
- All staff working in the study will have completed appropriate training to undertake the duties delegated to them by the Principal Investigator such an ICH-GCP and local SOP training.

8.3 Protocol Deviations

- A records of all protocol deviations should be maintained within the ISF.
- Any major deviations to the protocol will be reported to the sponsor within 24 hours of the occurrence to allow an impact assessment to be completed.
- Consideration will be given to the nature of the reported deviation, its causes, and the potential impact on the study.
- Where necessary, a deviation from the protocol may lead to an amendment to the protocol

8.4 Stopping Rules

It is not anticipated that the study will be stopped prior to its intended end-date. However, the study will be halted if:

- New information comes to light which means that the aims of the study are futile.
- Safety issues come to light regarding the intervention.
- Resources to conduct the study are no longer available.

8.5 Data Protection and Patient Confidentiality

Patient confidentiality will be maintained, and the study will be compliant with the requirements of the Data Protection Act 2018 in the following ways:

- The creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters.
- Secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media.
- Limiting access to the minimum number of individuals necessary for quality control, audit, and analysis.
- Dr Michael Hughes will act as the data custodian for the study data.
- The data will be stored until the final publication, after which time it will archived by Northern Care Alliance NHS Foundation Trust for 25 years from the date of the final publication.

Electronic patient records will be accessed by members of the direct care team in order to obtain patient's addresses and telephone numbers for recruitment purposes. The identification and screening of potential participants will be done by direct care team. This may include (where appropriate) sending letters to patients with the PIS. Once consent has been given, medical records may be accessed by either direct care team or research team to access study data.

Study data will be pseudonymised, having a study ID number that is linked to a study participant. Pseudonymised study data will be stored electronically on Trust or University of Manchester computers, and manually in locked filing cabinets. The details that link the study ID number to a study participant will be stored separately on password protected Trust computers alone.

Study data and material may be looked at by individuals from the University of Manchester, from regulatory authorities or from the NHS trust, for monitoring and auditing purposes, and this may well include access to personal information.

Electronic personal data will be stored on NHS computers which are encrypted, and password protected. Electronic pseudonymised data will be stored on the University of Manchester computers.

Paper based Case Report Forms (CRFs) will not contain participant identifiable data. Instead a study ID will be assigned to participants to ensure no identifiable data is available. It will be the responsibility of the local Principal Investigator (PI) to ensure the physical security of the CRF/research data during the trial.

All confidential data will be kept in a locked file room and electronic data will be password protected where only the Investigator and delegated staff have access.

After consent is obtained, patients will be given a unique code that will be used for data acquisition and analysis.

Pseudonymised data will be analysed on NHS or University computers by members of the research team.

Statistical advice/support will be provided by Research & Innovation, Northern Care Alliance NHS Foundation Trust, Clinical Sciences Building, Stott Lane, M6 8HD.

8.6 Indemnity

NHS indemnity applies for the management and conduct of the research. UoM indemnity applies to the design (protocol) of the study

9 Dissemination of Results and Publication Policy

It is anticipated that the results of this research will be disseminated in scientific journals, internal reports, conference presentations and via patient support groups.

The study and results may be promoted and publicised more widely via the 'Take Part' section of the Sponsor Trust's Research & Innovation website

Unless specifically requested, individual participants will not be informed of the results, as this is an imaging study and will not change patients' clinical management.

10 References

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