Study Title	**A feasibility study assessing combined pulsed dye and fractional CO_2 laser on burn scar outcomes versus factional CO_2 alone or standard care**
Short Title	**Combined Laser Impact on Scar Outcome (CLIPSO)**
Protocol Version	Version No. 1.7 March 8, 2023
Chief Investigator	Mr. Christopher Lewis
Sponsor	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder	Royal College of Surgeons of England Blond McIndoe Research Foundation
NUTH Reference	09905
IRAS Project Code	301064
Protocol Authors	Chris Lewis; Emma Hodgkinson

Trial Summary

	Name and Designation
	Chief Investigator (CI): Mr. Christopher Lewis, Consultant Burn Surgeon, Royal Victoria Infirmary, Newcastle upon Tyne
	Co-investigator: Dr. Emma Hodgkinson, Clinical Psychologist, Royal Victoria Infirmary, Newcastle upon Tyne
	Research Team Lead: Karen Smith Freeman Hospital, Newcastle upon Tyne
	Sponsor: The Newcastle upon Tyne Hospitals NHS Foundation Trust

Trial Title	A feasibility study assessing combined pulsed dye and fractional CO_2 laser on burn scar outcomes versus standard care
short title	CLIPSO (Combined Laser Improves Scar Outcome)
Clinical Phase	N.A.
Trial Design	Randomized controlled single, blinded study
Trial Participants	Adults with hypertrophic burn scars
Sample Size	10 to each treatment arm
Intervention	Combination pulsed dye and fractional CO_2 laser versus standard care
Follow up duration	8 months
Planned Trial Period	24 months
Objectives	
Primary	To determine if combined pulsed dye and fractional CO_2 laser treatment versus fractional CO_2 laser alone or standard scar therapy improves patient and observer reported scar appearance.
Secondary	To determine if combined laser treatment versus $AFCO_2L$ alone or standard scar therapy on burn scars improves patient reported symptoms of itch and psychological sequelae.

Abbreviations

AE	Adverse Event
AFCO$_2$L	Ablative fractional carbon dioxide laser
AR	Adverse Reaction
BBSIP	Brisbane Burn Scar Impact Profile
CI	Chief Investigator
GCP	Good Clinical Practice
HRA	Health Research Authority
HT	Hypertrophic
ICF	Informed Consent Form
IRAS	Integrated Research Application System
MSS	Manchester Scar Scale
NRBC	Northern Regional Burns Centre
NuTH	The Newcastle upon Tyne Hospitals NHS Foundation Trust
PDL	Pulsed dye laser
PIS	Patient Information Sheet
POSAS	Patient observer scar assessment scale
PPE	Personal protective equipment
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
TBSA	Total body surface area
VSS	Vancouver Scar Scale

1. Trial Summary

Hypertrophic (HT) scars following burn injury have an incidence ranging from 30-70% in reviewed data. These scars are red, lumpy and firm and have the potential to severity affect daily quality of life, causing itch, dryness, pain and restriction of joint movement during activities of daily living. Fundamentally, these scars may have a significant physical and psychological impact during rehabilitation, leading to stigmatization.

Advances in acute burn surgical care now means that more people survive major burn injuries, equating to more patients with HT burn scars. However, the optimum treatment for HT scar treatment remains to be elucidated. Different treatment modalities are available for scar treatment, including silicone, corticosteroid injection and compression. Laser therapy is a relatively new modality for the treatment of HT burn scars and is used in burn centres Worldwide for this capacity.

Two lasers show promise in the treatment of HT scars: the 595nm pulsed dye laser (PDL) and the 10,600nm ablative fractional carbon dioxide laser (AFCO$_2$L). Both lasers have been used individually and in combination for burn scar treatment. PDL is typically used to help reduce erythema and pruritus, while AFCO$_2$L is used to improve scar texture and thickness.

The aim of this study is to combine both laser treatments to investigate if the early use of combination laser treatment helps improve HT burn scar appearance (colour/texture) and associated symptoms including itch. Whilst these lasers have been used in combination before for the treatment of burn scars, this study is unique in that we will assess patient reported outcome measures, together with observer scar assessment tools.

A 10,600nm AFCO$_2$L (Lumenis) and a 595nm PDL (Candela) are the device to be used in this study. These lasers are both in routine use in the host institution and Worldwide for the treatment of scars and vascular lesions. They deliver precise high energy in short pulses to thickened scars and have a good record for safety and

outcomes. The Northern Regional Burn Centre has extensive experience in the use and delivery of both lasers and all health professionals involved have received the appropriate safety training.

Participants will be divided into three groups: control, $AFCO_2L$ only and combined PDL and $AFCO_2L$ treatment. Both laser groups will receive 3 treatments 6 weeks apart. Outcome measures will be conducted before laser treatment, 6 weeks after the last treatment of laser and 3 months post laser treatment. This feasibility study will serve to inform a larger multi-centre RCT in terms of study power, outcome measure frequency and whether treatment streams can be refined.

2. Background

Both PDL and $AFCO_2L$ are established to play a role in the treatment of post-burn HT scars[1]. Literature review identified 3 clinical trials surrounding the clinical response to $AFCO_2L$ alone and 4 papers reporting the combined use of $AFCO_2L$ and PDL for scar treatment.

Qu[2] reported on 10 participants treated with $AFCO_2L$ for post-burn HT scars. This uncontrolled prospective trial demonstrated measurable improvements on both Vancouver Scar Scale (VSS) and Patient Observer Scar Assessment Scale (POSAS) scar assessment at final follow-up (2 months after final treatment). Biopsy results showed a statistically significant reduction in mRNA expression of both TGF-β2 and 3 after treatment. Furthermore, bFGF mRNA expression was significantly decreased in the acute phase after treatment, whereas MMP-1 expression was increased.

The prospective case series of Waibel[3] aimed to highlight the potential augmentation of $AFCO_2L$ with the application of corticosteroid ointment immediately post-operatively. Of the parameters measured, texture received the highest improvement score, while dyschromia displayed the least. The overall improvement score was 2.73, which according to the authors, correlates to an improvement between 50-75% from baseline.

Ozog[4] conducted an uncontrolled, prospective study of 10 participants demonstrating a statistically significant improvement in VSS and POSAS at 2 months post treatment following AFCO$_2$L. Furthermore, a statistically significant decrease in type I collagen and a statistically significant increase in type III collagen was seen in the post-treatment biopsy specimens. Blinded analysis of post-treatment slides showed a statistically significant improvement in collagen structure post-treatment, with a change towards normal dermal framework.

Zuccaro[5] retrospectively reported on the use of combined PDL and AFCO$_2$L in the treatment of paediatric burn scars. This reported an improvement in VSS score following treatment but was uncontrolled with no further outcome measures.

Ouyang[6] conducted a controlled prospective trial comparing PDL alone with combined PDL and AFCO$_2$L for the treatment of HT scars. This study used VSS as the sole outcome measure, finding an improvement in scar thickness, redness and pliability, both with single and combined laser treatment.

Lei[7] combined PDL and AFCO$_2$L for the treatment of paediatric burn scars and reported the retrospetive uncontrolled data. Using unblinded POSAS assessments, significant improvements were found, but with no further outcome measures performed.

The reported biochemical and photomechanical processes associated with the clinical efficacy of AFCO$_2$L have improved our understanding of this treatment modality. However, there is a paucity of high-quality data regarding the combined use of PDL and AFCO$_2$L, both in terms of patient-reported outcome measures (PROMs), blinded observer scar assessment and skin biology. With robust and appropriate PROMs, this study hopes to yield data that informs our understanding of scar biology and remodelling in response to laser therapy and the clinical impact for patients.

3. Project Aim, Objectives & Hypothesis

3.1 Aim

To investigate if the early use of combination laser treatment helps minimise scar, improves patient satisfaction with scar appearance and associated symptoms versus single AFCO$_2$L treatment or standard care alone.

3.2 Objectives

- To determine the effect of combined PDL and AFCO$_2$L treatment on the subjective and objective clinical appearance of burn scars versus AFCO$_2$L alone or standard scar therapy.

- To determine if combined laser treatment versus AFCO$_2$L alone or standard scar therapy on burn scars improves patient reported symptoms of itch and psychological sequelae.

3.3 Hypothesis

Combined PDL and AFCO$_2$L treatment improves scar redness and pliability, reduces patient-reported scar-related distress and improves scar-related symptoms.

4. Study design

4.1 Type of research

Prospective, randomised, single-centre, single blinded (observer) controlled trial of combination PDL and AFCO$_2$L therapy to immature burn scars in adult patients with a burn scar between 1% and 5% total body surface area (TBSA), which meet inclusion criteria. This is a feasibility study to inform the development of a larger multi-centre RCT. In view of this, 10 patients will be recruited to each treatment arm and subsequent data analysis will reflect on wider RCT design and power.

4.2 Inclusion Criteria

- Participants > 18 years of age
- Hypertrophic burn scar ≥1% and 5% TBSA
- Scars which would ordinarily be managed by pressure garments and laser intervention
- All patients to be less than 3 months from discharge at point of recruitment.

4.3 Exclusion Criteria

- Participants < 18 years of age
- Pregnant or lactating females
- Facial scars
- Keloid scars
- Large (>5% TBSA) symptomatic hypertrophic scars not amenable to topical anaesthetic laser treatment
- Participants requiring general anaesthesia or block anaesthesia for laser treatment
- Scar of non-burn aetiology
- Previous topical or intralesional steroid treatment to study scar
- Mature (pale) scars more than 18 months following injury
- Inability to give informed consent
- Systemic glucocorticoid use
- Fitzpatrick skin types 4 - 6

5. Methods

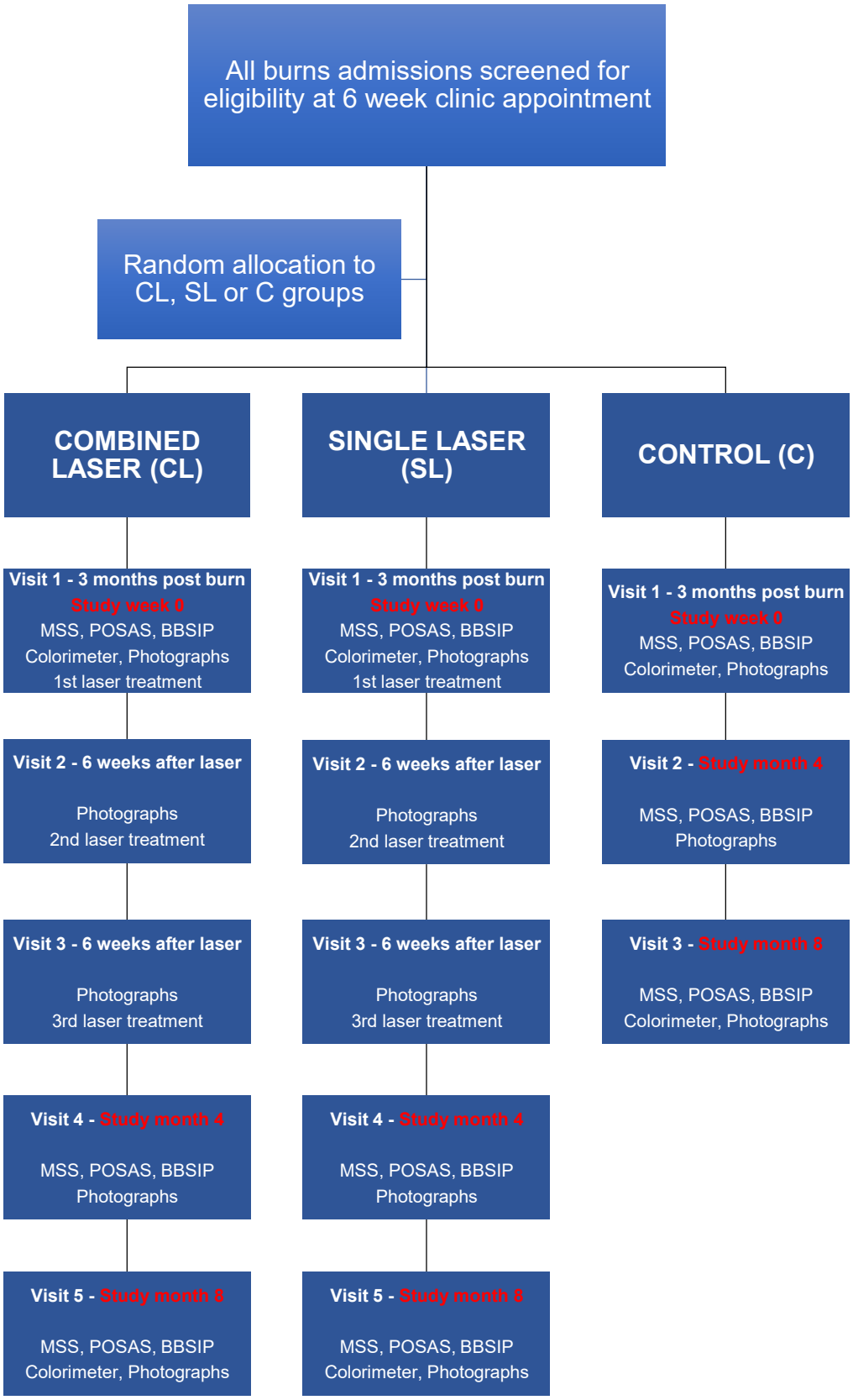
All adult patients treated at the Royal Victoria Infirmary Northern Regional Burn Centre will be screened for admission. Those patients who meet the selection criteria will be informed about the study and asked to participate at their six-week clinic appointment.

Each patient will be randomised to one of three groups: COMBINED LASER (CL), SINGLE LASER (SL) or CONTROL (C) group. A single hypertrophic scar site >1% - 5% TBSA is required for each patient. This scar size is deemed appropriate for topical local anaesthesia laser treatment as an outpatient.

In the event that the patient has multiple or large areas of hypertrophic scar, study participation will only be offered if laser treatment under topical local anaesthesia is possible and if the study participant consents to this. If the study PI feels this is not feasible, study participation will not be offered and the patient will continue with standard of care as provided by the host unit.

The rationale for this is that it is unethical to treat an area of hypertrophic scar within a large scar burden as standard of care in our host institution would be to treat all areas with AFCO$_2$L if deemed a suitable candidate. Furthermore, previous experience has illustrated that the subjective nature of PROMs makes it difficult for participants to provide meaningful answers if a small area of scar has been treated within a large scar volume; it is not possible to selectively comment on the daily physical/psychological impact of a small treated area if most of a limb/body is scarred.

Figure 1. Schematic diagram of the research design and stages



5.1 Intervention

All enrolled treatment arm patients (CL and SL groups) will receive laser under topical local anaesthetic due to the discomfort associated with the treatment. This approach is already employed in the host institution, whereby all patients undergoing AFCO$_2$L for small (<5% TBSA) areas are treated with topical LMX4 (4% lidocaine) cream for 60 minutes under occlusion prior to laser treatment.

1. COMBINED & SINGLE AFCO$_2$ LASER GROUP

In the combination laser group, PDL therapy will always be delivered first using the 595nm VBeam Perfecta (Candela) with the following settings:

10mm spot size (or proportionate to scar size and shape)
0.45 millisecond pulse duration
1.5Hz
5-7 Joule/cm^2 fluence
No overlap
Single pass
Dynamic cooling device 20/30 setting

The energy is selected to produce a degree of purpura/bruising during treatment without skin blanching. The skin response is instantaneous and should be dark purple to black. Whitening in the treatment area suggests over-treatment and is to be avoided. Once the desired response is seen, the entire trial scar is to be treated.

AFCO$_2$L therapy is delivered using the 10,600nm fractional CO$_2$ Ultrapulse laser (Lumenis) with the following settings:

30mJ – 50mJ micropulse energy
Rate 300Hz
5% density
DeepFX setting
No overlap
Single pass

A cool compress will be applied for 10 minutes following laser completion to dissipate any residual heat. All laser will be administered by the study PI who has laser experience and training.

Following laser delivery, vaseline emollient will be applied topically to all laser sites and dressed with non-adhesive silicone dressing. Patients are advised to remove these at home after 48 hours then apply paraffin emollient twice daily to all treated areas for two weeks. Patients are advised to avoid swimming for two weeks following laser. Following removal of dressings, all sites will be treated with standard scar treatments (pressure garment treatment, silicone, massage and moisturiser) by the scar therapy team.

The laser treatment will be delivered to intervention sites three times at six-week intervals. The time points for intervention have been determined based on a data from previous published research, as well as the clinical expertise of the PI who has conducted laser treatments and clinically evaluated individual response to therapy.

All laser settings will be recorded for each visit. At subsequent visits, participants will be asked to report any adverse effects of the treatment and laser will be delivered using the previous settings.
All participants in the treatments and control arms will receive standard scar therapy, which may include scar moisturisation, massage, silicone and pressure garments dependent on scar quality. Standard scar care will be delivered by a senior scar therapist. To avoid patient inconvenience and excess appointments, study visits will be coordinated with scar therapy team to occur at the same time.

5.2 Measures taken to minimise/avoid bias, including randomisation and blinding

Patients cannot be blinded to intervention in this study due to the nature of laser. In addition, sham treatment is not possible as study laser treatment results in localised heat, discomfort during laser delivery, bruising and a temporary grid of microscopic holes secondary to microthermal channel creation within the scar. These will be visible

to patients following dressing removal. The investigator conducting the outcome measures will be aware of the scar enrolled in the study but will be blinded as to whether it is in the control or treatment arm. Any indication of laser treatment will have settled prior to blinded scar evaluation at four and eight months following intervention (timepoints for independent objective scar evaluation). The study incorporates an interval of four weeks between the last laser session and blinded outcome measures, to ensure any sequelae of treatment have settled and negate observer bias.

5.3 Maintenance of any blinding records or randomisation codes and procedures for breaking codes

The Sealed Envelope online software (www.sealedenvelope.com) will be used to randomly allocate study participants to combined laser (CL), single laser (SL) or control (C) groups. The PI will select the scar and the anatomical location of the scar, and the site name (CONTROL, COMBINED LASER or SINGLE LASER) will be recorded immediately on a spread sheet. The area will be marked and photographed prior to treatment and following patient consent for medical photography images. There is no foreseen scenario whereby the laser site or the control site will be required to change. As this is a single blinded study, participants will know which treatment arm they are in negating the necessity to break blinding.

5.4 Data collection

1. COMBINED LASER (CL) group

Study visit 1	Study visit 2	Study visit 3	Study visit 4	Study visit 5
3/12 post burn Study week 0	**Study week 6**	**Study week 12**	**Study month 4**	**Study month 8**
1st laser session	2nd laser session	3rd laser session		
Ongoing scar therapy regime				
MSS			MSS	MSS
POSAS			POSAS	POSAS
BBSIP			BBSIP	BBSIP
Photographs	Photographs	Photographs	Photographs	Photographs
Colorimeter				Colorimeter

2. SINGLE LASER (SL) group

Study visit 1	Study visit 2	Study visit 3	Study visit 4	Study visit 5
3/12 post burn Study week 0	**Study week 6**	**Study week 12**	**Study month 4**	**Study month 8**
1st laser session	2nd laser session	3rd laser session		
Ongoing scar therapy regime				
MSS			MSS	MSS
POSAS			POSAS	POSAS
BBSIP			BBSIP	BBSIP
Photographs	Photographs	Photographs	Photographs	Photographs
Colorimeter				Colorimeter

3. CONTROL (C) group

Study visit 1	Study visit 4	Study visit 5
3/12 post burn Study week 0	Study month 4	Study month 8
Ongoing scar therapy regime		
MSS	MSS	MSS
POSAS	POSAS	POSAS
BBSIP	BBSIP	BBSIP
Photographs	Photographs	Photographs
Colorimeter		Colorimeter

5.5 Outcome Measures

The **Patient Observer Scar Assessment Scale (POSAS)** is a standardized measure whereby the patient rates all aspects of the appearance of a scar with the addition of questions regarding pain, itch and overall impression of the scar. The POSAS is reported to be reliable and valid scales that measure single-construct scar quality, as demonstrated by Rasch model analysis[2].

The **Manchester Scar Scale** objectively assess scar appearance will be used to assess the effectiveness of treatment of HTS. This assesses colour, contour, distortion, texture and sheen, and has been validated to show a strong correlation with micro and macroscopic features within a scar[8].

All patients will have standardized **digital clinical photographs** taken at all appointments. These will be performed with a digital camera on a grey/white background and will be deidentified. All photographs will record the following ID card including randomized number, study visit day, date and time of image capture[9].

The Brisbane Burn Scar Impact Profile (BBSIP) assessment questionnaire will be used to assess health-related quality of life in people with burn scars across three key domains: scar appearance (size, colour, contour), scar symptoms (painful, tight, itchy) and psychosocial impact (feeling self-conscious, bothered by scar). This has been extensively validated as an internationally applicable PROM[10-13]. As this

questionnaire contains questions about symptoms of depression and anxiety all participants who report concerns of depression and anxiety will be referred to the burns clinical psychologist within 24 hours.

Demographic information and standard clinical care will be recorded into an electronic database from information provided in electronic medical records. Variables recorded including age, gender, TBSA, length of stay, surgical intervention, data of pressure garment application, date of pressure garment removal, scar management interventions. This data will be accessed by the PI and nominated research team members. Data will be recorded alongside the participant ID for each patient in a pseudo-anonymised form.

Colorimetry using a digital colorimeter will provide data on scar erythema and pigmentation. Both parameters will be measured at enrolment and study conclusion to assess whether combination laser alters scar redness and pigmentation versus standard care. Measurements are taken in triplicate from a region of interest in the study scar, allocated by the PI. Control colorimeter measurements are taken from the contralateral area if It is scar-free. If there is no contralateral area free of scar, an alternate site of unscarred skin may be used and documented.

5.6 Sample size

Previous studies indicate a large effect size (Cohen's d 1.7). Therefore, for a size with 80% power and a 0.05 alpha, a sample size of 7 is required. We are proposing the conventional sample size of 30 patients for a feasibility study (10 participants per study arm). This will provide sufficient information to enable an accurate sample size calculation for use in a larger multicentre trial should a benefit be observed. If no benefit is seen to occur, then we can calculate the probability of having missed a potential benefit in our trial. This data will therefore inform the decision as to whether a future larger trial is warranted and necessary adjustments.

5.7 Follow-up duration

Following recruitment, patients will remain in the study for 8 months.

6. Consent

Consent to enter the trial must be sought from each participant only after a full explanation has been given, PIS provided, and time allowed for consideration and any questions they may have. Written participant consent will be obtained. If a participant is willing to enrol, but physically unable to sign an ICF (for example, burns to hands), there will be an option for witnessed verbal consent. This will be witnessed by a healthcare professional unrelated to the study. The right of the participant to refuse to participate without giving reasons will be respected. Participants are allowed to withdraw at any stage of the study without compromising their care in the hospital. Data already collected will be retained for use in the study, but patients will not be replaced if they withdraw from the project.
Written versions of the PIS and ICF will be presented to the participants detailing no less than:

- the exact nature of the trial;
- what it will involve for the participant;
- the implications and constraints of the protocol;
- the known side effects and any risks involved in taking part.

It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. The participant will be allowed one week to consider the information, and the opportunity to question the Investigator whether to decide whether they will participate in the trial.

Written informed consent will then be obtained by means of the approved ICF. The person who obtains consent must be suitably qualified and experienced, hold a valid GCP certificate and have been delegated to do so by the CI. A copy of the signed ICF will be given to the participant. The original signed form will be retained in the trial site file, with a copy added to the participants' medical notes, along with a copy of the PIS.

6.1 Participant Confidentiality

The PI must ensure that a participant's anonymity will be respected throughout the study and that their identities are protected from unauthorized parties. A participant's privacy and confidentiality will be maintained by the assignment of a unique identification number. The Investigator will keep a participant log showing codes and names of the participants. Confidentiality and protection of data will be maintained according to local regulatory requirements.

7. Statistical methods

Descriptive, univariate statistics will be used to describe the general characteristics of the sample. Differences between "Control" and "Intervention" groups will be examined using the Wilcoxon Signed Rank test, and a p value < 0.05 will be considered to indicate statistical significance. All statistical analysis will be conducted using PRISM.

8. Harms

Definitions

Adverse Event (AE): any untoward medical occurrence in a participant or clinical trial subject whether or not related to any research procedures or to the intervention
Non-serious adverse events which are not related to study procedures or to the intervention will not be reported in this study.

Adverse Reaction (AR): an adverse event judged as having a reasonable causal relationship to the intervention or to study procedures will be considered an Adverse Reaction. The existence of a 'reasonable causal relationship' will be judged by the researcher reporting the event. Any evidence or argument to suggest a causal relationship will also be reported.
In this study, adverse reactions will be reported regardless of seriousness.

Serious Adverse Event (SAE) and Serious Adverse Reaction (SAR): any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening

- Requires hospitalisation, or prolongation of existing in participants' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations.

An AE meeting any one of these criteria will be a SAE. An AR meeting any one of these criteria will be a SAR.

Reporting procedures

All related AEs and ARs should be reported to the CI or delegated individual. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the CI in the first instance, or delegated individual in the CIs absence. Severity of the adverse event should be reported along with the potential causality. It should also be documented as to whether it represents an unexpected or anticipated event. SAEs and SARs should be reported within 24 hours of becoming aware of the event.

Study conduct and management

The Investigators will ensure that this trial is conducted in accordance with GCP and all other relevant regulations. Overall responsibility of the study will rest with Christopher Lewis, Consultant Plastic Surgeon at NUTH.

The study will be conducted in accordance and with approval from appropriate regulatory authorities – HRA and REC – and local R&D department.

Research ethics approval

Approval will be obtained from the HRA and a REC through an IRAS application form. Local approval through NuTH R&D will also be obtained before accepting participants into the trial. The protocol, ICF, PIS and any proposed advertising material will be submitted to an appropriate REC, and host institution(s) for written approval.

Protocol amendments

The CI will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents. Protocol amendments will be transparently described in trial reports. A version control document will be recorded and saved using this template. The most recent protocol version will be stored in the trial master file. These will be approved by the HRA and REC as well as local R&D offices. These amendments will then be shared with all sites with required acknowledgement of change as well as proposed start date.

End of trial

The end of trial for an individual participant is defined as being on completion of their final study visit 9 months following burn injury. The approving REC requires notification of the end of trial within 90 days of its planned completion or within 15 days if the study is terminated early. The responsibility for submitting the Clinical Study Report will lie with the Chief Investigator and Sponsor.

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