1.0 Protocol title & version details

1.1 Titles

Full Title

A Randomised Controlled Trial to Compare Epidermal Grafting with Split Skin Grafting for Wound Healing

Short Title

Epidermal grafting in wound healing

1.2 Protocol version details

Version 1.2

October 18 2016

1.3 Names, roles and contact details

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Principle researchers	1) Mr Muholan Kanapathy, Research Fellow, UCL Division of Surgery and Interventional Science, Fourth floor, 74 Huntley Street, London, WC1E 6AU 2) Miss Nadine Hachach-Haram, Specialist Registrar, Department of Plastic and Reconstructive Surgery, Royal Free Hampstead NHS Trust Hospital, Pond Street, London, NW3 2QG 3) Miss Nicola Bystrzonowski, Specialist Registrar, Department of Plastic and Reconstructive Surgery, Royal Free Hampstead NHS Trust Hospital, Pond Street, London, NW3 2QG
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Host Trusts & Study Site(s)	1) Mr Afshin Mosahebi, Consultant Plastic Surgeon and Senior Lecturer, Department of Plastic and Reconstructive Surgery, Royal Free Hampstead NHS Trust Hospital, Pond Street, London, NW3 2QG 2) Professor Keith Harding, Head of Wound Healing Research Unit, Cardiff University, School of Medicine, Upper Ground Floor, Heath Park, Cardiff CF14 4XN
Clinical Laboratory	UCL Division of Surgery & Interventional Science, Centre for Nanotechnology & Regenerative Medicine, Royal Free NHS Trust Hospital Campus, Pond St, London, NW3 2QG

2.0 Signature Page

Signatures of all healthcare professionals involved in the study are documented below:

Chief Investigator & Clinical Academic Supervisors	**Professor Toby Richards, Professor of Surgery and Consultant Vascular Surgeon, UCL**
	_____ _____
	Signature Date
	Mr Afshin Mosahebi, Consultant Plastic Surgeon and Senior Lecturer, Royal Free Hampstead NHS Trust Hospital
	_____ _____
	Signature Date
Principle researchers	**Mr Muholan Kanapathy, Research Fellow, UCL Division of Surgery and Interventional Science**
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	Miss Nadine Hachach-Haram, Specialist Registrar in Plastic Surgery, Royal Free Hampstead NHS Trust Hospital
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	_____ _____
	Signature Date

3.0 Contents page

4.0 Summary

4.1 Aim(s) and reason of the study

Split thickness skin grafting is the normal standard of care for wound closure. However, this is an invasive procedure and associated with pain also there can be additional donor site morbidity. Epidermal grafting is an emerging clinical alternative that is gaining clinical practise. Epidermal grafting (EG) is an alternative method of autologous skin grafting that 'harvests' a finer layer of skin than traditional Split Skin grafting (SSG). This potentially results in less pain and reduced donor site morbidity but only delivers several cell layers to the wound so may be less effective at healing a wound. It is not known if EG is an effective alternative to SSG.

Further the mechanism to achieve wound healing may be different. EG promotes wound healing by expressing growth factors that accelerates wound healing and encourages keratinocyte migration. Whereas SSG is a transplant of several skin layers that integrated to the existing wound bed as a formal skin covering.

We wish to compare these two clinical practises; epidermal grafting and split thickness skin grafting in wound healing.

4.2 Primary and secondary objectives

Our primary objective is to determine the efficacy of epidermal grafting to split thickness skin grafting in wound healing at 6 weeks and 3 months.

Our secondary objective is to gain information on the biology of wound healing with EG and SSG, specifically to compare the expression of cytokeratin (keratinocyte marker) and Connexin 43 (gap junctional protein) before and after grafting.

4.3 Description of methods and assessments

Research participant design and methodology

1) The Population of patients will be those referred, following assessment and review, by a Consultant Plastic Surgeon for split thickness skin grafting or Epidermal grafting. Patients will be identified, from both the outpatient clinic and inpatient referrals.
2) Patients will undergo a 'run in phase' to ensure the wound bed is ready and appropriate for grafting. This will include negative microbiology. Wound will be deemed 'ready' by two trial clinicals. Baseline three dimensional wound photographs will be taken.
3) Patients will be offered participation in the study, provided with the Patient Information Sheet (PIS) and will be allowed time (at least 24 hours) prior to obtaining informed consent.
4) Patient will be consented and randomised to either an epidermal graft or a split thickness skin graft group.
5) The interventional procedures will be undertaken within 7 days of randomisation
6) Baseline assessment will include;
    a. Wound assessment using the Wound Assessment Form (Appendix 4)
    b. Photographs of the donor site and wound site
    c. Wound exudate sampling.
    d. Punch biopsies at the wound edge and the centre of the wound.
7) Patient will then receive treatment (either epidermal graft or split thickness skin graft) and immediate follow up assessments
    a. Pain scores relevant to the procedure
    b. Time of the Procedure – start to finish
8) Patient will be reviewed at day 7 ± 2 post grafting in an outpatient plastic surgery clinic
    a. Wound assessment using the Wound Assessment Form (Appendix 4)
    b. Photographs of the donor site and wound site
    c. Wound exudate sampling.
    d. Punch biopsies at the wound edge and centre of the wound.
9) Wounds will be reviewed weekly in the outpatient clinic for 6 weeks or until wounds are healed.
    a. Health resource utilisation will be collected of dressing changes.
    b. Photographs of the donor site and wound site

c. Documentation of any adverse events

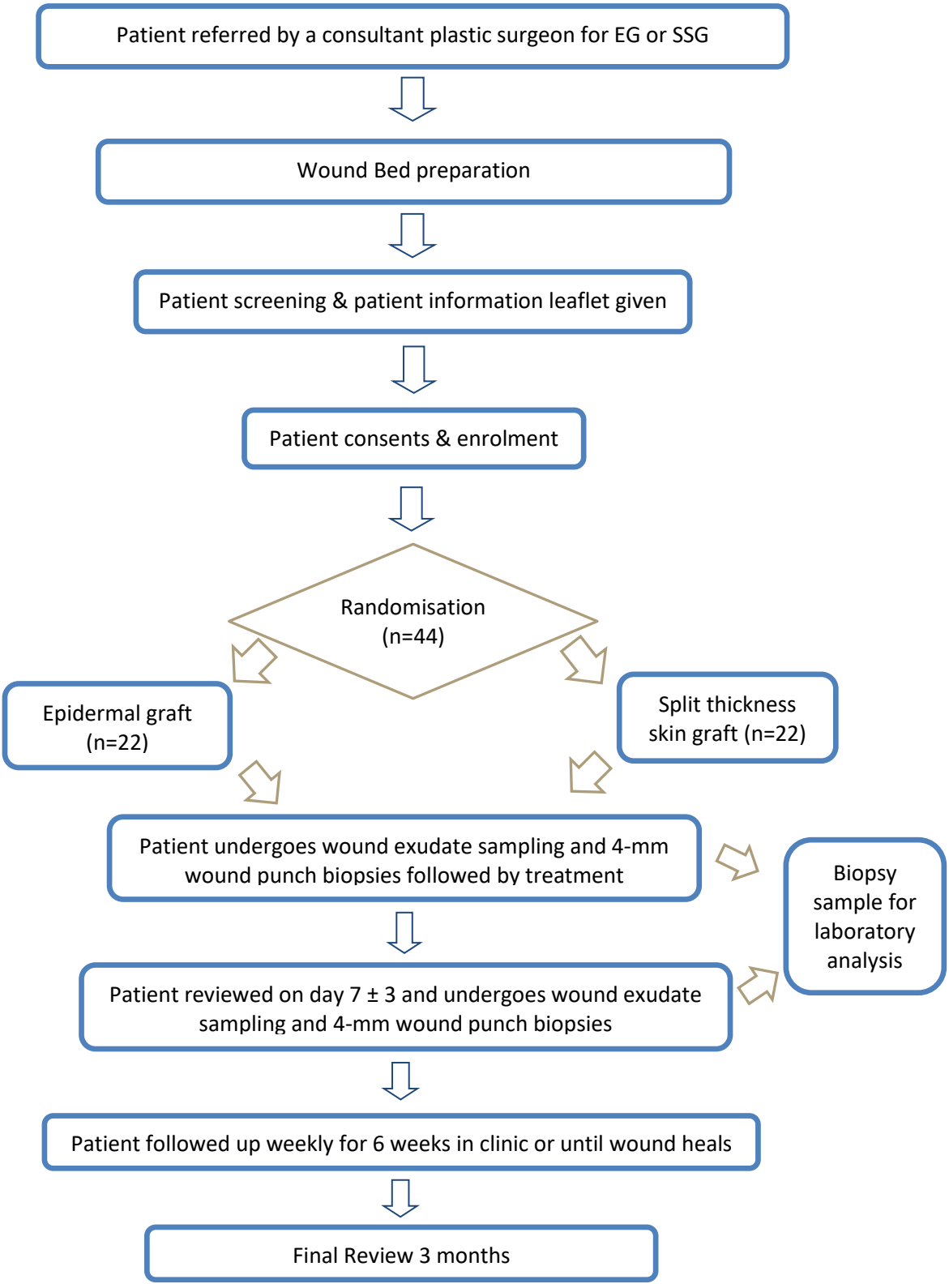
10) 6 week review

a. Wound assessment using the Wound Assessment Form (Appendix 4)
b. Photographs of the donor site and wound site
c. Patient's satisfaction using the Patient Skin Graft Satisfaction Questionnaire (Appendix 5)
d. Documentation of any adverse events

11) 3 month review

a. Health resource utilisation will be collected of dressing changes
b. Photographs of the donor site and wound site
c. Patient's satisfaction using the Patient Skin Graft Satisfaction Questionnaire (Appendix 5)
d. Documentation of any adverse events

Figure 1.0 Flow chart illustrating patient journey throughout the study



Wound bed preparation

All patients will be reviewed by a consultant plastic surgeon and assessed then referred to the department of plastic surgery for SSG or EG. Normal clinical practise is that all wounds will be assessed clinically and prepared with either negative pressure wound therapy (NPWT) or appropriate wound dressings to achieve wounds with healthy granulating bed. Wound swabs will be performed to ensure no infection as per normal clinical practise. During this time period of wound bed preparation patients will be flagged to the research team. When the wound bed is deemed 'ready for grafting' agreed between two treating clinicians, patients will then screened and where appropriate be offered a patient information sheet for inclusion into the trial. Once the patients are ready for intervention, following review by the study team, patients will undergo informed consent and randomisation.

Ppunch biopsy procedure – technical aspects

Prior to any intervention, the patient will be assessed clinically to confirm 'inclusion and exclusion criteria' are met (see Section 8.0) and informed consent form will be completed (see Appendix 2). Wound assessment will be documented in the 'wound assessment & biopsy form' (see Appendix 4).

Punch wound biopsies (4mm) will be taken from two locations, at the centre of wound and at the wound edge, after administering adequate local anaesthesia. This procedure will be done at the start of the study and at day 7 post-grafting. The punch biopsy procedure is a routine dermatological procedure, and is a safe and efficient method of obtaining a tissue sample appropriate for laboratory research. Punches are circular cutting instruments of various diameters (4mm in this case) that cut cylindrical pieces of tissue from the skin to the underlying fat. The punch is withdrawn and the specimen removed using small forceps and scissors. The specimen is then placed in a specimen pot containing paraformaldehyde and transferred to the laboratory. Following the procedure, any bleeding (if present) will be controlled by direct pressure over the site of biopsy.

Study investigators are experienced clinicians and care will be taken to ensure good quality wound biopsy samples, appropriate for histological analysis and further laboratory studies. Study documentation and biopsy procedure will take approximately 5-10 minutes.

Epidermal graft harvesting – technical aspects

Prior to grafting, the wound and donor sites are cleaned by the operating surgeon. The harvesting device will be applied to the donor site (thigh) for 40-50 minutes to harvest the epidermal graft as per existing normal clinical practise. The harvested epidermal graft will then be transferred onto the wound using Adaptic Touch (non-adhering silicone dressing, measuring 5cm x 5cm) or another appropriate dressing. The wound is dressed with Aquacel (hydrofiber dressing) followed by gauze or another appropriate dressing as deemed by the treating clinician. The wound will be secured with either a crepe bandage if appropriate or mefix. The donor site will be dressed with Tegaderm (a semi permeable, adherent dressing) or another appropriate dressing as deemed by the treating clinician. The wound will be reviewed on day 7 ± 3 post-grafting as per normal clinical practise.

Split thickness skin grafting – technical aspects

Patients will undergo this procedure in the operating theatre or in minor operations designated clinic room under general or local anaesthetic. The wound will be initially debrided by the treating clinician. The split thickness skin graft will be harvested from the thigh using an air dermatome, set to cut at the thickness of 5-10/1000 inch. The split thickness skin graft will then be applied onto the wound and dressed with Adaptic Touch or another appropriate dressing as deemed by the treating clinician. The donor site will be dressed with Kaltostat (Alginate dressing) or another appropriate dressing as deemed by the treating clinician, with a 2.5cm overlay beyond the wound margin and secured with mefix. As per standard clinical practise, the graft will be checked at day 7 ± 3.

Laboratory studies methodology summary:

1. We will determine the type and concentration of growth factors expressed by the epidermal graft and its response to the wound, both pre- and post-grafting, comparing it with split thickness skin graft.

2. We will compare the expression of cytokeratin (keratinocyte marker) and Connexin 43 (gap junctional protein) before and after grafting.

Follow up protocol

Participants are reviewed at day 7 ± 3 post grafting and then weekly, for 6 weeks. On every follow-up visit, photographs and measurements of the wound and donor site will be taken.

Pain score as reported by patient will be recorded using Numerical Rating Scale at day 1, 2, 3, 4, 5, 6, 7, 14, 21, 28, 35, and 42. A validated 'patient skin graft satisfaction questionnaire' (see Appendix 5) will be completed by participants at the end of the study. In all cases two questionnaires will beundertaken one for the donor site and one for the wound itself.

As per current clinical practise, patients are allowed to change the dressing at home every 3-7 days after the first week review.

5.0 Background

5.1 Literature search and review of epidermal graft

Epidermal grafts are made of multi-layered keratinocytes, in which a variety of other cell types with specialised functions are embedded, such as the melanin pigment-producing melanocytes, the immune-competent Langerhans cells, the neuroendocrine Merkel cell and the basal layer contain epidermal stem cells (1). In normal wound healing, keratinocytes begin to migrate from the wound edges within 24 hours to the wound bed where they proliferate and form new epithelium (2).

Traditionally, various, relatively cumbersome, techniques have been used to harvest EG, however these harvesting techniques have not been easily reproducible, limiting its potential to be used in the clinical setting (3).

CelluTome (from Acelity), a novel automated EG harvesting device, produces an array of epidermal microdomes immediately available for transfer to the recipient site. Migrating keratinocytes synthesise and deposit a variety of extracellular matrix components, such as laminin, fibronectin, and type IV collagen (4). In addition, numerous growth factors are also produced, namely, the epidermal growth factor (EGF), transforming growth factor alpha (TGF-a), and heparin-binding growth factor (HB-EGF) which act on epidermis to promote wound healing (5). During this process, epidermal grafts simulate bioengineered skin, stimulating the endogenous process of wound healing that has yet to be fully understood.

In a similar study protocol we have previously found that gap junctional protein, Connexin 43 (Cx 43), plays a pivotal role in wound healing (REC reference: 11/LO/1483, IRAS Project ID: 79542). Abnormal Cx43 expression results in delayed wound healing (6). Cx43 is normally down-regulated in wound-edge keratinocytes in the first 24-48 hours as they change to a migratory phenotype. In abnormal rat skin with increased Cx43 expression, wound-edge keratinocytes fail to change to a migratory phenotype, resulting in a bulb of non-migratory keratinocytes. By inhibiting the up-regulation of Cx43, rat wounds healed at a normal rate. Our recent clinical pilot data suggests that greatly elevated levels of Cx43 protein are a feature of both keratinocytes in a wide variety of human chronic wounds (pressure, venous, diabetic and unhealed surgical

wounds) (7). These observations are supported by the findings of both Abdullah et al. who reported elevated gap junctional coupling in cultures of fibroblasts and Brandner et al. who reported the presence of Cx43 in keratinocytes at the edge of chronic wound biopsies (8, 9).

Connexins are regulated by growth factors affecting the Connexin levels, cellular distribution, channel open probability and conductance/permeability (10). It is therefore plausible that the epidermal grafts express an array of growth factors which encourage the migratory activity of keratinocytes by down regulating the expression of Connexin 43 and accelerating wound healing. Understanding the cellular biology will enable a better evaluation of the efficacy of epidermal grafts in acute and chronic wound management.

5.2 Justification

The total cost of wound management to the NHS is estimated to be about £2.3-3.1 billion per year (11) with up to half a million patients suffering from debilitating peripheral vascular disease and wounds significantly affecting their quality of life (12).

Most wounds are managed in the outpatient setting with protocols that vary according to geography, institution and speciality. Currently, wound requiring split thickness skin grafts often requires hospital admission, at least 12 hours, a period of immobility for some patients, attentive donor site wound care and pain management. Cutting edge alternatives such as tissue engineered skin grafts carry their own challenges; namely the cost, relatively long cultivation time, and are limited to specialised facility.

This study evaluates the efficacy of EG, as an alternative to current wound management therapy, SSG. In a pilot study carried out in our centre (unpublished data), we noted that this technique offers a method of autologous skin harvesting with minimal or no pain and a scar free donor site. Moreover, complete wound epithelialisation was achieved while maintaining patient independence. Therefore, this device has the potential to save NHS resources, by eliminating the need for theatre space and a hospital bed, and result in better Patient Reported Outcomes Measures.

6.0 Specific aims of the study

Our primary endpoint is to determine the efficacy of EG in wound healing at 6 weeks. This will be done via measurement of the wound at each review, using expert clinical assessment, the trust wound assessment criteria, and analysis of photo diaries. An independent blinded analysis of the photo diaries will be carried out by 2 plastic surgeons. Inter and Intra rater reliability will also be assessed.

Our secondary objective is to determine the type and concentration of growth factors expressed by the EG, as well as to compare the expression of cytokeratin and Connexin 43 before and after grafting.

7.0 Study design

A prospective, randomised, multicentre study, in 2 parallel groups. The centre involved is the Royal Free Hospital, London. The sample size will be 44 patients, 22 patients in the EG group and 22 patients in the SSG group. The study participants are to be recruited between October 2015 and June 2018 and participants in both groups are to be followed up for 6 weeks. Groups are to be compared with respect to age, sex, BMI, and comorbidities.

Study type		:	Investigational
Estimated enrolment		:	44 patients
Study start date		:	1 October 2015
Estimated study end date		:	1 June 2018
Study design:	Allocation	:	Randomised
	Endpoint	:	Efficacy study
	Intervention Model	:	Parallel Assignment
	Primary Purpose	:	Treatment

Randomisation process

After obtaining informed consent, patients will be randomly assigned to either the epidermal graft group or split skin graft group using computer randomisation.

8.0 Study participants

Subject inclusion and exclusion criteria for the study are shown in Table 1 below:

Inclusion Criteria	**Exclusion Criteria**
1. Male or female 2. Age 18-90 at time of consent 3. Wound measuring more than 1cm x 1cm and lesser than 5cm x 5cm (1% TBSA) 4. Wound with clean, healthy granulating bed, with minimal adherent slough 5. Patient understands and is willing to participate and can comply with weekly visits and follow-up regime	1. Wound with active infection 2. Wound at plantar of the foot 3. Patients unsuitable for Split Skin Grafting in the opinion of the investigator 4. Previous history of excessive bleeding associated with surgical biopsies or trauma 5. Allergies to tegaderm (and other dressings used in the study) 6. Known uncontrolled Diabetes Mellitus, as measured by an HbA1c > 10%. 7. Presence of one or more medical conditions, including renal, hepatic, hematologic, active auto-immune or immune diseases that, would make the subject an inappropriate candidate for this ulcer healing study 8. Patient not fit for surgery (ASA classification > 4)

Table 1: Inclusion and Exclusion Criteria for Study Participants

9.0 Study setting

Participants will be recruited at one centre, namely the Royal Free Hospital (RFH), London.

Trial will be conducted in accordance to the Declaration of Helsinki and the recommendations of Good Clinical Practice.

10.0 Participants recruitment and consent

10.1 Recruitment of participants

All patients will be reviewed by a consultant plastic surgeon and assessed then referred to the department of plastic surgery for SSG or EG. During normal routine wound care in preparation for intervention patients will be flagged to the research team and where appropriate be offered a patient information sheet and screened for inclusion into the trial. Once the patients are ready for intervention, following review by the study team, patients will be offered participation in the study and informed consent will be obtained.

10.2 Gaining participant consent

Written informed consent will be sought prior to enrolment in the study. This process will include an explanation of the aims, methods of skin harvesting and subsequent wound management, anticipated benefits and potential hazards of the study. Patients are given sufficient time (offered a period of 24 hours or more if needed) to consider whether they wish to participate.

Consent will also be obtained for serial clinical photography of the wound and donor site for each review, to document the condition and wound healing process. There will be no financial payments offered to patients.

11.0 Outcome measures

Primary outcome measures:

- Wound healing at 6 weeks post grafting.

- Time for donor site healing.

Secondary outcome measures:

- Time for wound healing
- Pain score as reported by the patients at day 1, 2, 3, 4, 5, 6, 7, 14, 21, 28, 35, and 42 using Numerical Rating Scale.
- Patient satisfaction for the donor site measured using a Patient Skin Graft Satisfaction Questionnaire.
- Patient satisfaction for the wound measured using a Patient Skin Graft Satisfaction Questionnaire.
- Incidence of adverse events.

12.0 Data

12.1 Data to be collected

Prior to grafting, wound will be assessed and recorded in the 'Wound Assessment and Biopsy Form' (Appendix 4). Details on patient's co-morbidity, previous surgery to the wound, number and type of previous wound dressings will be recorded. Photographic documentation of the wound and donor site is performed before and after grafting, as well as at each wound review.

The appearance and measurement of the wound is recorded at each visit. Pain score as reported by the patients will be recorded at day 1, 2, 3, 4, 5, 6, 7, 14, 21, 28, 35, and 42. Data on number of outpatient visits and cost for each visit is recorded. Patient satisfaction will be measured at the end of the study using a 'Patient Skin Graft Satisfaction Questionnaire' (Appendix 5).

12.2 Data handling and record keeping

The multidisciplinary healthcare professionals at the outpatient clinic will have access to participants' personal data to enable them to provide patient care. The data extracted for the purposes of this study would be anonymised. All personal data extracted will be stored on trust computers, which can only be accessed by research investigators, and are password protected.

The NHS computers and university computers, which will store the data, are encrypted and kept in a secure building with swipe card access. Access to all computers will be via secure login. All personal and study data will be stored on NHS secure servers and will be password protected with restricted access to unauthorised individuals. All handling, processing and storage of personal identifiable data and study data will be in accordance with the Data Protection Act 1998 and the NHS Code of Confidentiality.

We will store research data generated by the study for five years at UCL. The chief investigator will have long term access to research data after the study has ended.

13.0 Study assessment

The primary outcome analysis is made based on the measurement of the wound taken at each visit. The wound and donor site will be assessed using a standardised wound assessment tool, the 'PUSH Tool' (Appendix 4), at each visit. The wound area will be measured with a sterile centimetre ruler as length of long axis x greatest width perpendicular to long axis, as per normal clinical practise. Wound healing at 6 weeks and time for donor site healing will be recorded. The PUSH Score for the wound and donor site will be statistically analysed. If the primary intervention had failed at week 6 ± 2, re-grafting and repeat of biopsy as per protocol will be considered after discussing with patient. Failed intervention is defined as increasing wound size or failure of 50% reduction in wound size at week 6 ± 2.

Image analysis

The wound and donor site will be photographed at each visit using a 3-dimensional camera, LifeViz (from Quanticare), to obtain high quality, accurate and standardised images for analysis. These images will be stored in patient's photo diary.

14.0 Statistical Considerations

14.1 Sample size

We will recruit a total of 44 patients into this study, with 22 patients randomised into each study arm. Preliminary data suggests that both techniques offer same healing rate at 6 weeks post grafting, however donor site morbidity is present in 40 % of patients with split thickness skin graft while only 5% is seen in patients with epidermal graft. Sample size calculation with power of 80% at 5% significance level indicates that 22 patients per group are necessary

14.2 Statistical analysis

All analysis will be conducted according to the intention-to-treat principle with the use of SPSS version 22 (IBM, Armonk, NY, USA). Patients are evaluated for analysis if they received a study treatment. If the clinical course cannot be fully evaluated, the last point of visit is considered as the last data analysed. Baseline characteristics of the two groups will be recorded. The continuous variables will be compared using Student t-test. The categorical variables will be compared using Pearson's chi-square or Fisher's exact test depending on the number of events.

The proportion of wounds healed with each treatment will be compared using chi-square test or Fisher's exact tests depending on the number of events. Mean time to wound healing will be determined on the bases of the number of days until complete re-epithelialisation, using Kaplan-Meier analysis of cumulative wound healing, followed by a log rank test.

Secondary outcomes will be compared between groups using a chi-square test for categorical variables. Non-normally distributed continuous variables will be compared using Mann-Whitney U test. A p value of less than 0.05 will be considered significant and all tests will be two-sided.

15.0 Subject Compliance & Withdrawal of Subjects

15.1 Subject Compliance

Participants who are undergoing an operation will be verbally re-consented at the time of surgery to confirm they wish to remain in the study and for the biopsies to be performed.

15.2 Withdrawal of Subjects

Subjects will be withdrawn from the study under the following circumstances:

- Participant develops serious life threatening illness and is admitted to hospital.
- Participant who has given informed consent, loses capacity to consent during the study for any other reason.

All subjects withdrawing from the study will be recorded along with reasons for withdrawal and details of planned follow up.

16.0 Ethical Considerations

16.1 Benefits, risks and burdens to study participants

Information obtained from this study will benefit wider scientific research in particular with regards to the role of grafting in wound healing. The information obtained from this study may improve future treatment of patients.

The risks to study participants will be minimized. This study is to be undertaken in a university teaching hospital. Two small 4-mm punch biopsies will be taken, by an experienced surgeon, one from the participants' wound edge and the other from the centre of the wound, before treatment and 7 days post grafting. Contraindications to undergoing this procedure are clearly specified in the exclusion criteria. Should a complication of biopsy occur, immediate treatment can be provided as the patient is in the surgical environment. Participants will be asked prior to informing their GP of involvement in the study. Patients will be reviewed weekly at the outpatient specialist clinic.

Participants in the study will have the opportunity to discuss their current wound-healing progress with study investigators. To minimize bias and conflict of interest, participants' future treatment options will not be discussed by investigators.

16.2 Approvals from relevant groups

Patients, service users, carers and members of the public will be involved in the research process through Royal Free Hospital patient focus group discussion. For patients attending these groups, it will provide opportunity for them to express their views about this research project and the current service. They will also receive published information regarding the results of this study. Patients who do not attend these groups will be informed of the groups' involvement and will also be invited to take part in the study. Specifically we have asked patients undergoing EG or SSG about the protocol to be studied and their willingness to participate in such a trial.

Formal approvals are to be sought from NHS/HSC, Trust Research and Development offices and Research Ethics committee.

17.0 Finance, Insurance & Harm

17.1 Finance details

This study is part of Dr Muholan Kanapathy's doctoral research project. The study itself is not funded specifically. MK is funded from UCL by his supervisor Mr Toby Richards.

17.2 Insurance details

University College London holds insurance to cover participants for injury caused by their participation in the clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

17.3 Cover for non-negligent and negligent harm

The study will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office. Hospitals selected to participate in this clinical study shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

18.0 Reporting and Dissemination

The results of the study will be reported and disseminated in peer reviewed scientific journals, conference presentations, website/online publications as well as internal reports. Reporting will be based on CONSORT guideline for reporting randomised trial. All publications will be forwarded to participants.

19.0 List of relevant references

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