Secondary intention wound healing following excision of keratinocyte cancers on the lower leg (HEALS2)

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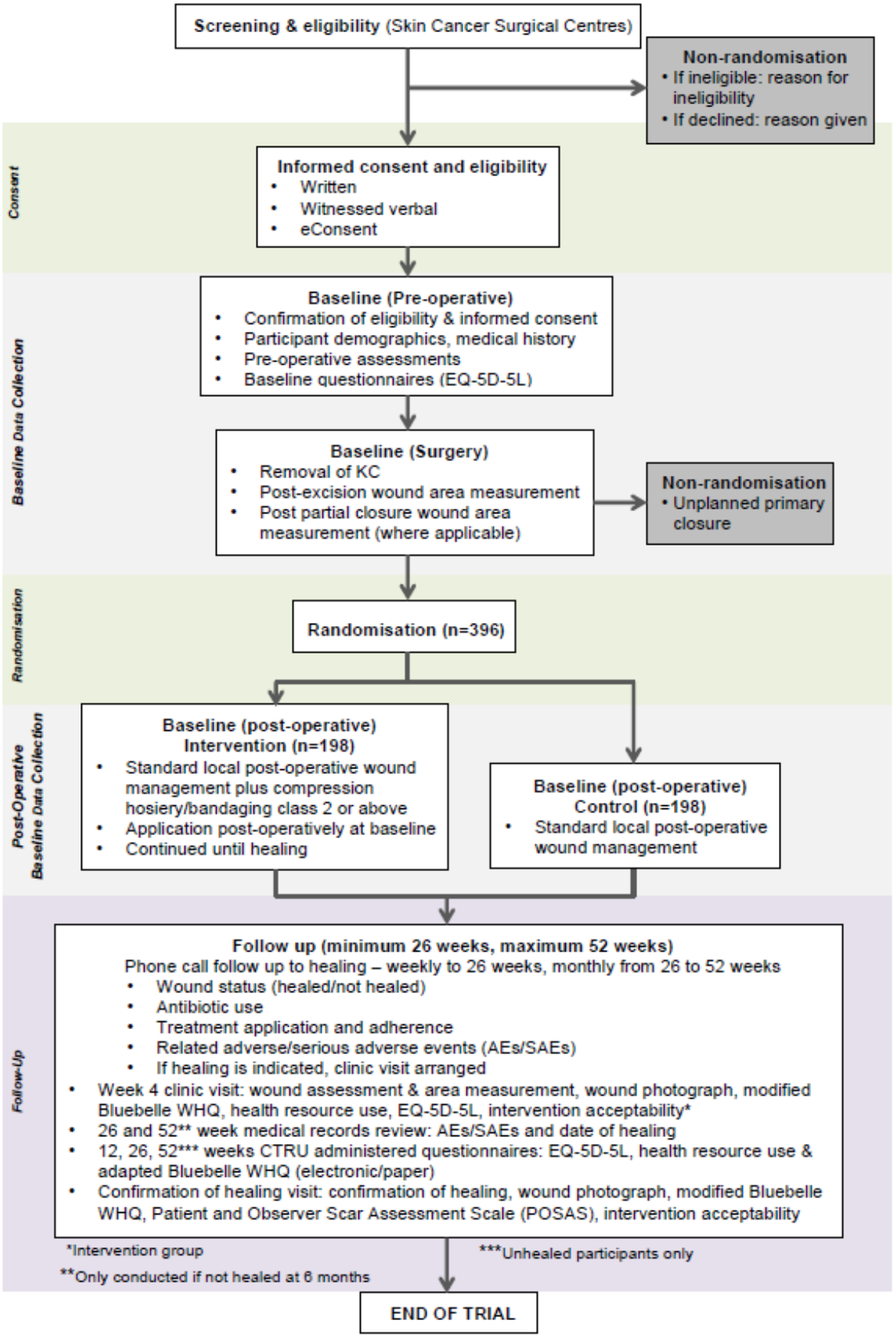


4. GLOSSARY OF TERMS/DEFINITIONS

ABPI	Ankle-brachial Pressure Index
AE	Adverse Event
APL	Authorised Personnel Log
BSDS	British Society for Dermatological Surgeons
CEAC	Cost-Effective Acceptability Curves
CEAP	Clinical-Etiology-Anatomy-Pathophysiology
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence Interval
CONSORT	CONsolidated Standards Of Reporting Trials
CRF	Case Report Form
eCRF	Electronic Case Report Form
CRP	Clinical Research Practitioner
CT	Compression therapy
Non-CTIMP	Non-Clinical Trial of an Investigational Medicinal Product
CTRU	Clinical Trials Research Unit
CVD	Chronic Venous Disease
DAM	Decision Analytic Model
DMEC	Data Monitoring and Ethics Committee
EQ-5D-5L	EuroQol - 5 Dimension 5 Levels Questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
HBSI	Healing by secondary intention
HR	Hazard Ratio
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICD	Informed Consent Document
ICER	Incremental Cost-Effectiveness Ratio
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention-to-Treat
KC	Keratinocyte cancer
LICTR	Leeds Institute of Clinical Trials Research
MRC	Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NRES	National Research Ethics Committee
PeRSEVERE	PRincipleS for handling end of participation EVEnts in clinical trials Research
PH	Proportional Hazards
PI	Principal Investigator
PIS	Patient Information Sheet
PIN	Personal Identification Number
POSAS	Patient and Observer Scar Assessment Scale
PPI	Patient and Public Involvement
PROGRESS	PROGnosis RESearch Strategy
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial

RDE	Remote Data Entry
REC	Research Ethics Committee
REDCap	Research Electronic Data CAPture
RGF	Research Governance Framework
RHCP	Registered Healthcare Professional
RUSAE	Related Unexpected Serious Adverse Event
RR	Relative Risk/Risk Ratio
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SC	Standard care
SCSC	Skin Cancer Surgical Centre
SFT	Secure File Transfer
SOP	Standard Operating Procedure
TMG	Trial Management Group
TMP	Trial Monitoring Plan
TSC	Trial Steering Committee
UKDCTN	United Kingdom Dermatology Clinical Trials Network
WHQ	Modified Bluebelle Wound Healing Questionnaire

5. BACKGROUND

5.1 Rationale

The number of people with skin cancer is increasing due to demographic changes and social behaviours. Our patients are an aged population and high post-operative complication rates are reported in this very elderly patient population. While compression therapy (CT) is currently used for some patients, there is variation in practice and clinical equipoise exists so there is an opportunity to evaluate this 'simple' intervention

5.2 Wounds

The annual prevalence of acute and chronic wounds increased by 71% between 2012/13 and 2017/2018, with an estimated 3.8 million patients with a wound (excluding surgical wounds healing within 4 weeks) managed by the National Health Service (NHS) in 2017/18 and an annual cost of £8.3 billion(1). Surgical wounds (of over 4 weeks) accounted for 14% of these wounds, and in turn surgical wounds on the lower limb account for 15% of all surgical wounds healing by secondary intention(2). Wounds healing by secondary intention impact upon quality of life, with considerable patient burden due to pain, exudate, repeated visits for wound dressings, possible infections and inability to work and/or socialise with long term effects of scarring and discomfort(3).

5.3 Skin Cancer

Skin cancers are common and numbers are increasing year on year due to demographic changes and an increasingly aged population and social change including sun exposure(4). Skin cancers including malignant melanoma and **keratinocyte cancers (KCs)** in the UK are projected to cost the NHS over £180million per year and impose significant demands on primary, community and secondary care services(5, 6). KC including basal cell and squamous cell carcinomas are very common (incidence 245.1/100 000 or 210,000 diagnosed annually)(7) but have high cure rates with surgical excision and primary closure/skin graft/flap or partial/no closure and healing by secondary intention.

Surgical wounds, healing by secondary intention (HBSI) after excision of KC lesions on the lower leg (approximately 12% of all KCs, 26,000/year(7)) provide particular clinical challenges. First, due to anatomical location and lack of skin laxity, many are not amenable to primary closure or local flaps(8). Second, people undergoing surgery for KC on the lower leg are typically elderly with concurrent mobility limitations, peripheral vascular/venous disease and local oedema, factors which delay healing and increase risk of complications including infection(2, 9, 10). Third, post-operative oedema due to the inflammatory process is a common sequela of surgical wounds which normally resolves within a few days in most body sites. However, in the lower leg, the cumulative effect of peripheral vascular/venous disease and gravity delays this resolution and is likely to compromise wound healing.

In considering this patient cohort and common condition we identified:

a) lack of outcome data as patients are discharged from secondary care follow-up before healing
b) absence of a recognised guideline for the post-operative management
c) clinical uncertainty about the use of compression as a primary post-operative intervention to promote time to healing and reduce complications.

The lack of evidence to underpin practice was acknowledged by the United Kingdom Dermatology Clinical Trials Network (UKDCTN) who have supported a programme of trainee led research to inform this grant application. The work has included: a 2014(8) and 2021 survey of clinicians(11); UKDCTN funded trainee led cohort feasibility (12, 13); UKDCTN Patient and Public Involvement (PPI) focus group and a trainee led systematic review as detailed in the following sections.

5.4 Patient Burden

The UKDCTN funded HEALS cohort (n=53) was undertaken to assess the feasibility of performing a large-scale definitive phase III trial and is the first study to investigate time to healing, infection and serious adverse events (SAEs) following excision of KC on the lower leg in patients without compression. The cohort study

recruited from 9 centres across the UK. Participants were adults, without significant arterial disease, who had planned excision of KC on the lower leg and expected to have a wound HBSI without post-operative compression.

Demographically, participants and non-registered patients were similar, demonstrating that the sample was representative of the target patient population. Patients received routine follow-up care and data was collected weekly either at standard care (SC) clinic visits or weekly phone calls to the patients. Variables collected post-operatively included details of clinical assessments, wound treatments, medications, healing status. Patient pathways were defined including the frequency, type of professional and care setting for follow-up contacts.

The study population had a median age of 81 years, 21% had mobility limitations and whilst we excluded patients with severe venous incompetence 73.6% had visible or palpable signs of venous disease. Reflecting risk factors for delayed wound healing, the study identified considerable patient and NHS burden with median time to healing 81 days (95% confidence interval (CI) 73-92), wound infection 30.2% (n=16), hospitalisation for infection/cellulitis 5.7% (n=3),unhealed at 6 months 7.5% (n=4) with healing status unknown for 7.5% (n=4) (12).

5.5 Why Compression Therapy

Compression therapy has been established by primary research/systematic review evidence as the primary/first line treatment strategy for healing of venous leg ulcers and also informed which compression systems are most effective (9, 14). Compression is now in common clinical use for the treatment of venous leg ulcers and has transformed venous leg ulcer management, reducing the burden of wounds.

Mechanistically compression reduces oedema and improves venous return and tissue oxygenation. Given the high levels of underlying venous disease and the normal occurrence of post-operative oedema due to the inflammatory process it is proposed that lower leg wounds HBSI may benefit from compression in a similar manner. However, it is also recognised that CT can be resource intensive (although the use of compression hosiery is now enabling patient self-care) and can sometimes be difficult to apply and be uncomfortable for the patient. When our patient group were presented with different compression options, most members agreed that bandages might be hot and/or uncomfortable but those who had experienced oedema/infection or delayed healing were less concerned with these issues. It is therefore essential to assess the clinical and cost effectiveness of compression as a primary post-operative intervention in terms of reduced time to healing and secondary outcomes including infection.

5.6 Clinical Practice and Equipoise

In order to promote healing, post-operative CT is used by some Dermatology surgeons. Respondents(n=109) of a trainee led 2014 survey of British Society for Dermatological Surgeons (BSDS) identified that 56.7% sometimes used compression and 30.5% always used compression post-surgery for these wounds(8). There was, however, considerable variation in the Class of CT and duration – with some respondents applying compression for short periods (2-6 weeks) and others until healing. In a 2021 survey of potential research centres by our group(11), equipoise remained evident with 16/21 dermatology centres indicating a willingness to randomise to both SC and SC plus CT.

5.7 Existing Evidence

Our group has undertaken a systematic literature review(10) and identified no randomised controlled trials (RCTs) comparing no compression with compression for wounds HBSI after excision of KC on lower leg. We identified only 2 cohort studies with reported mean time to healing for no compression (n=53) of 81 days(12) and compression (n=10) of 50 days(15). Unpublished local audit data at a participating centre also reported 88% (22/25) of patients with compression healed within 6 weeks. From a safety perspective we also identified a retrospective cohort n=366(16) which reported that patients who had post-operative compression were less likely to develop complications vs those without compression (OR 0.67: p=0.74), but time to healing was not reported.

Compression therapy has been rigorously evaluated in the venous leg ulcer population(17). And there is significant evidence that CT increases healing rates when compared with no compression, with improved

time to healing (5 studies; 733 participants; hazard ratio (HR) 2.17 (95%CI 1.52-3.10)) and complete healing (8 studies; 1120 participants: relative risk/risk ratio (RR) 1.77 (CI 1.41-2.21)) with no impact upon adverse events (AEs)(14). Systematic review evidence and trials also indicate that: multi-component systems are more effective than single component systems; elasticated systems are more effective than non-elastic and; within Class bandage systems and hosiery are similarly effective e.g. 4 layer bandage, 2 layer bandage and 2 layer hosiery(18) which has improved patient and clinician choice and associated adherence. For example, the most recent Health Technology Assessment (HTA) study(9) found no difference in healing between (Class 3) 4-layer high compression bandaging or two layer hosiery, whilst hosiery was easier to apply, less bulky and use more likely to be sustained.

From a patient's perspective, in the venous leg ulcer population, there is evidence that some patients do not always adhere to their CT. A qualitative study has been recently published which explored barriers and facilitators to CT (19). Findings suggest that adherence is multi-factoral. Issues such as the choice of therapy, patient lifestyle and service organsiation appeared to contribute.

5.8 PPI Focus Group

Our UKDCTN funded focus group comprised 8 patients with previous experience of lower limb excision of KCs. We discussed their experiences and exchanged ideas about important outcomes. They felt it was acceptable to be randomised to either SC or SC plus CT. We discussed the follow-up option of weekly contacts, and the group felt this was acceptable. This informed the data collection schedule. They felt capturing information about complications such as infection, the time the wounds took to heal and the appearance of scar/healed wound were important, hence relevant data will be collected. Our PPI group also felt that, given the choice, most would prefer to wear hosiery than bandages. They also felt hosiery increased opportunities for self-care.

5.9 Summary

CT is applied to reduce leg oedema and promote healing for lower limb KC wounds HBSI, but there is clinical equipoise, variation in practice when used, and no supporting evidence of effectiveness. Our PPI work has also shown that compression is acceptable to this group of patients.

6. AIMS AND OBJECTIVES

6.1 Aim

The aim of this pragmatic RCT is to evaluate the clinical and cost effectiveness of CT in the healing of surgical wounds HBSI following excision of lower limb KCs.

6.2 Primary Objective

The primary objective is to compare the time to healing from randomisation, between SC or SC plus CT.

6.3 Secondary Objectives

Secondary objectives will compare groups for:

- Incidence of infection as measured by modified Bluebelle Wound Healing Questionnaire (WHQ) (20) until healing
- Numbers of days participants prescribed antibiotics until healing
- Scar quality as measured by Patient and Observer Scar Assessment Scale (POSAS)(21)
- Safety events including related complications and hospitalisations until healing (maximum 52 weeks post randomisation)

- Cost effectiveness via a within-trial and decision analytic model assessed from a payer perspective measuring patient health related quality of life in Quality Adjusted Life Years (QALYS) meeting updated Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 updated reporting guidance(22)
- Health-related quality of life (HRQoL) as measured by EuroQol 5 Dimensions 5 Levels questionnaire (EQ-5D-5L) to 26 weeks post randomisation (52 weeks where applicable, for unhealed participants only).
- The relationship between post-partial closure wound area, type of partial closure method, and time to healing

6.4 Exploratory Objectives

- Explore associations between short-term wound area reduction between baseline and 4 weeks post randomisation and time to healing
- Explore patient acceptability and factors affecting adherence to randomised treatment

7. DESIGN

The trial is a multicentre, prospective, Phase III, parallel group, open-label, randomised, controlled trial with embedded internal pilot, blinded endpoint assessment, economic evaluation, minimum 26 week/maximum 52 week follow-up comparing time from randomisation to complete surgical wound healing (epithelialisation) between control (SC) and intervention (SC plus CT) groups. See Section 10 for further details of treatment/intervention and Section 15 for further details of measurement and confirmation of the primary outcome, including blinding measures.

Randomisation will take place immediately post-operatively (in theatre or post-operative recovery area). 396 participants will be randomised in a 1:1 allocation ratio (198 per group) to SC or CT using a minimisation algorithm stratifying by:

- Centre
- Immediate post-excision wound area (6.0cm^2 or less/more than 6.0cm^2 prior to any partial closure (23))
- Wound depth (excision to fat/excision to fascia or periosteum)

Randomisation will be performed via a central, independent, secure 24-hour automated randomisation system provided by Leeds CTRU using a minimisation algorithm (including a random element) to ensure allocation concealment.

Participants will be recruited from UK centres which offer skin cancer surgery centre services including district general and teaching hospital settings.

Internal pilot
In line with funder requirements the trial monitoring includes an internal pilot. The internal pilot will assess patient pathways, recruitment rate and equipoise across all sites in the first 9 months of recruitment. Equipoise will be assessed by;

- Review of screening log data overall and by centre to assess reasons for not participating including for example:
    - eligible patients were not approached including reasons
    - participant ineligible as compression indicated by clinical team
    - eligible patients did not consent to take part, in particular, whether the patient wants/does not want compression
- Review of immediate post-randomisation allocation adherence by trial arm including proportion of participants who don't receive treatment as per randomisation (control or compression) and reasons

The internal pilot progression criteria detailed below are based on the average recruitment/centre/ month over a 9-month period, number of centres opened and recruitment total. A recommendation for continuation or continue (remedial actions required) will assess each of the targets below interchangeably, acknowledging that not all criteria are required to be green for trial delivery to be considered viable.

	Recruitment/centre/month	Number of centres opened	Total number of participants recruited	Adherence with SC + compression at 4 weeks post randomisation
Green	At least 0.81	12	At least 50	At least 80% of participants allocated to SC+compression arm are wearing allocated treatment most days at 4-week time point
Amber	0.41-0.81	9-11	25-49	At least 60% to <80% of participants allocated to SC+compression arm are wearing allocated treatment most days at 4-week time point
Red	<0.41	<9	<25	Less than 60% of participants allocated to SC+compression arm are wearing allocated treatment most days at 4-week time point

Supplementary data from the pilot phase period on non-adherence with randomised allocation and primary endpoint completeness will be reviewed by the independent Data Monitoring Committee (DMEC). Recommendations from the DMEC will be considered alongside assessment of performance versus progression criteria targets and screening data in consultation with the Trial Steering Committee (TSC) which will feed into the internal pilot phase report submission to facilitate decision-making by the Funder about whether the main trial should proceed (either unmodified or with a modified protocol and remedial actions such as increasing the number of recruiting centres, additional centre engagement activity, revised recruitment projections based on observed recruitment rates).

8. ELIGIBILITY

All adult patients attending a Skin Cancer Surgical Centre (SCSC) will be screened for suitability by the attending clinical/research team if they have a KC on the lower leg which is planned to be excised and HBSI. The lower leg is defined as 'below the knee, including the ankle and foot but excluding the toes'. Patients will be consented pre-operatively. Screening logs will be maintained to review reasons not eligible or unable/declined consent.

8.1 Patient Inclusion Criteria

1. Aged ≥18 years
2. Planned excision of suspected KC on lower leg with healing by secondary intention
3. Ankle-brachial pressure index (ABPI) ≥ 0.8 or toe pressure of > 60 mmHg
4. Informed written/witnessed verbal/eConsent.

8.2 Patient Exclusion Criteria

1. Planned primary closure/skin graft/flap
2. Receiving/planned compression for another indication
3. Severe venous incompetence e.g. Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification C5 or C6 (24)
4. Contraindication to at least medium compression(18-24mmHg)
5. Unable to comply with CT
6. Suspected to have a non-KC diagnosis or require further surgery
7. Previously taken part in HEALS2

NB If a patient consents with the expectation that the wound will be HBSI but surgery is completed with primary closure, then randomisation will not take place. The likelihood of this happening will be explained to the patient during the informed consent process.

Post-randomisation exclusion: In the event that a patient is identified post-operatively as needing further surgery e.g. having melanoma, they will be excluded post-randomisation as the care pathway is complex and requires secondary and potentially radical surgery and our follow-up questions would be both inappropriate and distressing.

9. RECRUITMENT PROCESS

9.1 Recrutiment Setting

The recruitment setting will be secondary care centres undertaking surgery for skin cancer and may comprise dermatology surgery and/or plastics surgery services (SCSC) with surgery scheduled in outpatient clinic and day case surgery facilities.

Research centres will be required to have obtained local confirmation of capability and capacity, undertake a site initiation meeting with the CTRU and receive a CTRU green light prior to the start of recruitment into the trial.

Reflecting variation in referral, diagnosis and surgical scheduling, patients are referred from a healthcare professional to a centre offering SCSC. The referral will usually suggest a potential diagnosis of a KC on the lower leg and be accompanied by photographs. Several pathway options may then be available for identifying eligible participants depending on local arrangements as follows:

Telephone/video diagnostic assessment and scheduled surgery
Clinical pathway: Patient is contacted by a member of the attending clinical team via telephone or videocall for confirmation of suspected diagnosis of KC and appraisal of the most likely surgical management (i.e., excision with closure/flap/graft; excision with healing by secondary intention). Where surgery is indicated, capacity to consent for surgery is assessed (standard surgical NHS practice). Patients with capacity provide consent to surgery (e-Consent/ verbal/ written) and surgery is scheduled.

Research Pathway: Where the attending clinical team identifies potential trial eligibility (ie KC on the lower leg and planned HBSI), they will discuss the trial with the patient and offer further information. Assenting patients will receive full study information by email/post/online link at either the index telephone/video clinical appointment by a member of the attending clinical team or (subject to verbal assent for provision of their contact details) at a follow-up telephone/video appointment at a date and time convenient to the patient by a member of the clinical research team.

Face-to-face diagnostic assessment visit and surgery scheduling
Clinical pathway: Patient is contacted by a member of the attending clinical team via telephone/letter inviting them to attend a clinical assessment/pre-operative visit. Consent for surgery is obtained at this visit.

Research pathway: At this visit, assenting patients who are identified by the attending clinical team as potentially eligible will be either: a) seen in clinic by a member of the clinical research team and study information provided. Consent (eConsent or paper consent) may be taken at this time or any time prior to their subsequent surgery; b) subject to verbal assent for provision of their contact details receive full study information by email/post/online link at a follow-up telephone/video appointment at a date and time convenient to the patient by a member of the clinical research team.

Same day diagnostic assessment and surgery

Clinical pathway: Consultants screen referral letters and patients are contacted by the attending clinical/administration team by telephone and letter to confirm a clinic date for assessment and where indicated, same day consent for surgery and surgery.

Research pathway: At initial consultant screening of referral letters, a short study information leaflet will also be included with the appointment letter with contact details for the local research team. Patients may then contact the research team to discuss the study, their eligibility and consent process. Additionally, all patients attending the same day assessment and surgery clinics with be screened for trial eligibility and where indicated, provided with study information by the attending clinical team or a member of the local research team. Study information will be given during the same day assessment/surgery visit and patients will consider study participation within the period of the clinic visit and if wishing to participate will be required to provide consent pre-operatively.

9.2 Eligibility Screening

Participating research sites will be required to complete a screening and non-randomisation log of all patients presenting with a lower leg KC with planned HBSI, who have been considered for the trial but have not been recruited into the study. Documented reasons for ineligibility or declining participation will be collected and closely monitored by the CTRU as part of the regular review of recruitment progress. Non-randomisation logs should be returned to CTRU on a monthly basis. The following anonymised data will be collected on the non-randomisation log:

- Age
- Gender
- Ethnicity
- Date screened
- Reason not suitable for randomisation OR
- Reason declining participation
- Deprivation score
- Preferred language

9.3 Informed Consent and Eligibility

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996.

The assessment of eligibility will be confirmed, and the informed consent process will be undertaken by the PI or Registered Healthcare Professional (RHCP) who is GCP trained and has been approved by the PI as detailed on the Authorised Personnel Log (APL). The PI or designate will confirm consent by countersigning the informed consent form.

Where a participant is required to re-consent or new information is required to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU. The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study and are out-with SC at the participating site (including the collection of identifiable participant data). The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without

prejudicing his/her further treatment and has been provided with a contact point where he/she may obtain further information about the trial.

Assenting patients will be seen/contacted by a member of the HEALS 2 clinical research team who will provide a full verbal explanation of the study and Patient Information Sheet (PIS) for the patient to consider. This will include detailed information about the rationale, design and personal implications of the study. Following information provision, patients will have as long as they need to consider participation and will be given the opportunity to discuss the study with their family and other healthcare professionals before they are asked whether they would be willing to take part in the study. Assenting patients will be formally assessed for eligibility and invited to provide informed consent, which must be obtained prior to surgery.

Informed consent can be taken either (i) as remote e-consent (ii), remote verbal consent over the telephone/videocalling, (iii) face-to-face during a SCSC visit on a paper form or using the e-consent format. The mode of informed consent used will depend on patient and participating site preference, and their accessibility to a device to support the e-consent process. Patients will be provided with information on the e-consent process to help inform their decision on the method of consent.

Remote eConsent Principles

Patients who choose to consent using remote e-consent will provide verbal consent for their initials, date of birth, and email address to be disclosed to CTRU through a Research Electronic Data Capture (REDCap) system. If the patient does not consent to this disclosure, they will be unable to use the remote e-consent process and a paper based process will be followed and a convenient time will be arranged to complete a face-to-face paper/e-consent process.

Remote eConsent
A copy of the PIS will be provided to the patient prior to the remote e-consent telephone/videocall or their clinic visit, by email or by post (according to service pathway and patient preference). Following information provision and patient agreement to participate in HEALS2, the researcher will verify the participants' identity by asking the patient to confirm their initials, date of birth and email address and assent for disclosure through the e-consent system.

The patient will receive a link to and open the e-consent application, the researcher will discuss each point on the consent form, with the patient. The patient will be asked to complete all questions and add a signature (electronically signing a form is an act completed by clicking a button to confirm the completion of the form), then submit the form. The researcher will open the form and complete the sign-off. Where it is not possible for the patient to complete all questions and sign the form during the call, they will be asked to do this as soon as possible after the call. The researcher will follow up with the patient in the event the form is not completed. When completed by the patient,the researcher will open the form and complete the sign-off. The participant will receive an electronic copy of the consent form, or the researcher may download and post a copy of the completed form if requested.

Remote Verbal Consent
For participants unable to complete remote e-consent (e.g. electronic device accessibility), the researcher will read each statement on the consent form to the patient, initialling and signing the paper consent form on behalf of the patient. A copy of the consent form signed on behalf of the patient will then be posted/emailed to the patient.

In Person (face-to-face consent during a visit to the SCSC)
For participants who choose to complete in-person consent, this can be done through the e-consent application (as above) or by taking standard written informed consent .

Witnessed verbal consent may be used for patients who have capacity to consent but are unable to physically sign the paper form. An appropriate witness would be a family member or friend of the patient, or another member of the patient's healthcare team who is not directly involved in the research study.

Following information provision, patients will have as long as they need to consider participation and will be given the opportunity to discuss the study with family and other healthcare professionals before they are asked whether they would be willing to take part in the study. Patients will also be provided with a contact point where he/she may obtain further information about the trial.

A record of the consent process detailing the date of consent and those present will be detailed in the patients' healthcare records. Where a paper consent form exists, the original form will be filed in the Investigator Site File (ISF) at the participating centre, a second copy included in the healthcare record (as per local practice) and a third copy will be returned to the CTRU via Secure File Transfer (SFT) system. Where eConsent has taken place, local practices will dictate record keeping.

Patients who provide informed consent who subsequently lose capacity will be withdrawn from the trial.

Full informed consent will be obtained for **all** participants prior to randomisation. Participants who have consented prior to the day of surgery will be asked to verbally reconfirm consent to continue in the trial, prior to randomisation.

9.4 Randomisation

Informed written/witnessed verbal consent/e-consent for entry into the trial must be obtained prior to randomisation. Following confirmation of informed consent and eligibility for randomisation participants will be randomised by an authorised member of staff at the research site. Randomisation will be performed centrally using the CTRU automated, secure, 24-hour randomisation service which can be accessed via the

web. To randomise using the web-based system a staff site email address, site code and Personal Identification Number (PIN) will be required. Authorisation codes and PINs will be provided by the CTRU to access the randomisation service. These codes will only be issued once a site has been fully approved and all the necessary documentation has been received at CTRU.

Baseline demographic, Quality of Life (QoL) and medical history questionnaires should ideally be completed pre-operatively, prior to randomisation. However, if time does not allow, these can be completed post-surgery but pre-randomisation. A record will be made of when the questionnaires were completed.
Randomisation will be performed on the day of surgery, immediately post-operatively, by the research nurse/RHCP who will need to complete the Randomisation case report form (CRF) prior to the time of accessing the randomisation service, as the following information will be required:

- Participant details including initials, date of birth, and NHS number
- Site code
- Confirmation of informed consent
- Confirmation the post-operative wound is healing by secondary intention i.e. not primary closure or grafted
- Confirmation of formal eligibility for randomisation
- Confirmation of completion of baseline questionnaires
- Confirmation of completion of baseline assessments (post-operative wound length and width measurements and wound depth category)

Randomisation will use a minimisation algorithm incorporating a random element to ensure groups are well balanced for the following factor and participant characteristics, details of which will also be required for randomisation:

- Immediate post-excision wound area (prior to any partial closure: 6.0cm^2 or less/more than 6.0cm^2(23). Wound area will be calculated by the randomisation application using the elliptical method (25) from maximum length and width measurements provided by site.
- Wound depth (excision to fat/excision to fascia or periosteum)
- Centre

Participants may only be randomised into the trial by an authorised member of staff at the trial research site, as detailed on the APL.

Online Access for 24-hour Randomisation:
https://lictr.leeds.ac.uk/webrand/

After trial randomisation the research site will:

- Add the unique participant identification (ID) number to all CRFs
- Return a copy of the completed paper consent form to CTRU (if applicable)
- CTRU will email a Participant Randomisation Notification to the research site.

Participants will be randomised in a 1:1 treatment allocation ratio to one of two groups respectively:
i) Standard care (SC) alone
ii) SC plus compression therapy (CT)

Following randomisation (on the same day the randomisation process is completed) the research site will:

- Apply the randomised treatment strategy

- Provide each participant with a trial ID card (paper format or a pdf sent electronically) and inform them to keep this with them at all times and present to the attending clinical team if their wound has healed.
- Provide each participant with a RHCP letter to present when required during a SC appointment.
- Ensure that participants are notified of their SC appointment dates.
- Notify the patient's General Practitioner (GP) of participation in the trial.

Participants may only be randomised into the trial once.

10. TREATMENT/INTERVENTION DETAILS

SC throughout the study is provided through routine attendance at outpatient clinics, community wound clinics, community nursing services, GP and practice nurses, patient self-care or informal care provider (as per local practice).

10.1 Standard Care (SC) Pathway

For SC, the participant will receive the best SC provided by the local recruiting centre.

Day of Surgery: Patients attend the SCSC, are reassessed and consent for surgery is confirmed by the surgeon.Under sterile conditions (i.e. skin preparation/drapes), excision of KC is undertaken following administration of local anaesthetic. The surgeon may perform partial closure (e.g., purse string suture) and then the wound is dressed as per local practice. Immediate post-operative dressings may include haemostatic products such as Alginate dressings. In some centres a soft dressing retention bandage is applied with or without padding.

The wound may be monitored for up to 30 minutes and then the patient is discharged with a standard information leaflet which includes contact phone details in case of concern about bleeding, infection or other AE.

Post-Operative Care and Wound Management: This will be according to local policies/protocols/pathways. Our feasibility cohort (12, 13) indicates that patients are typically seen twice weekly initially for 2-4 weeks in the SCSC. Subsequently visits reduce to weekly with further tapering over time with visits continuing in either secondary care or in primary or community care on a planned or ad hoc basis until healed. Dressings are applied through a combination of self-care, SCSC clinical team, by practice nurses or community wound clinics (for patients who are mobile and able to attend their local GP premises or clinics) and community district nurses (for immobile patients requiring home visits). Following referral to primary or community care for dressing changes, treatment may be provided at any of the following settings: GP surgery, health centre, community wounds clinic or patient's own home. Additional advice regarding mobility/activity, emollient use and skin care may be provided by the attending clinical teams.

10.2 Randomised to SC

Standard care will be carried out as above.

10.3 Randomised to SC and Compression therapy (CT)

Patients will receive SC as above plus CT.

Compression will be initiated in the SCSC and continued throughout the episode of wound treatment until healing.

Trial CT will deliver pressures between 18 – 40 mmHg at the ankle i.e., CT will comprise a Class 2 or Class 3 below knee hosiery or bandage system(18). It will be applied to the lower limb, excluding the toes and finishing below the knee. A list of approved compression therapies will be available.

Compression choice (ie hosiery vs bandage system, Class 2 vs Class 3) will be based on patient preferences and clinician's discretion from a research informed(9, 14, 18) trial approved product list; the rationale for choice will be reported e.g. ability to self-manage, compression related discomfort, patient lifestyle, amount of oedema, pain, frequency of dressing changes, planned follow-up pathway. The underlying principle is the provision of compression until healing.

Where randomised to CT, compression will be applied as soon as possible and additional information provided in respect of the CT. Frequency of hosiery change will be determined by ability to self-care and/or frequency of SC wound dressing changes. Frequency of bandage system changes will be determined by frequency of SC wound dressing changes.

10.4 Withdrawal of Treatment

In line with usual clinical care, cessation or alteration of treatment strategies at any time will be at the discretion of the attending clinical team or the participants themselves. Participants who do not receive or complete the protocol treatment strategies due to participant request or clinician decision are **NOT** classed as full withdrawals. **Follow-up assessments will continue and CRFs will continue to be completed according to the protocol schedule unless consent for follow-up is withdrawn** (see Section 10.5).

10.5 Withdrawal of Consent

Clinician withdrawal: clinicians involved in the trial should not withdraw participants from the trial unless it is harmful for the participants to continue or a patient is deemed to have lost capacity. Where there is a clinician withdrawal no further follow-up data will be collected past the point of withdrawal and data collected up to the point of withdrawal will be used in the analysis.

Please note that where a patient is identified post-operatively as needing further surgery e.g. having melanoma, they will be withdrawn and classified as a post-randomisation exclusion (see Section 8).

Participant withdrawal (full or partial): Participants may withdraw consent from the trial at any time without explanation. The PI or delegate should make every effort to ensure that the specific wishes of any participant who wishes to withdraw from further involvement in the trial are defined and documented using the withdrawal Case Report Form in order that the correct processes are followed by the CTRU and site. Withdrawal forms must be completed and returned to CTRU within 7 days.

Participant withdrawal will be classified as follows:

a) Withdrawal of consent to the study treatment strategy only
b) Withdrawal of consent to the study treatment strategy and wound photography (if initially consented to wound photography)
c) Withdrawal of consent for wound photography only
d) Withdrawal of consent to the follow-up schedule (including photography) but the participant is willing to have/has completed the randomised treatment strategy and is willing for further information to be collected from healthcare records.
e) Withdrawal of consent to the study treatment strategy and the follow-up schedule (including photography), but the participant is willing for further data to be collected from healthcare records.
f) Withdrawal of consent to the follow-up schedule and further data collection (including photography and via healthcare records) but the participant has completed the randomised treatment strategy.
g) Withdrawal of consent to the study treatment strategy, the follow-up schedule (including photography), and all further data collection via healthcare records.

Table 1. Participant Withdrawal Scenarios

Scenario	Withdrawal from study treatment strategy	Withdrawal from wound photography	Withdrawal from follow-up schedule and associated data collection (including photography)	Withdrawal from data collection from healthcare records
a)	X			
b)	X	X		
c)		X		
d)		(X)*	X	
e)	X	(X)*	X	
f)	n/a - completed	(X)*	X	X
g)	X	(X)*	X	X

** Note that withdrawal from wound photography is implicit in withdrawal from follow-up schedule and associated data collection, here indicated by (X)*

For a), b) and c) completion of CRFs will continue as per the protocol schedule and all of the participant's data will be used in the trial analysis.

For d) and e), after participant has withdrawn consent from follow-up schedule, data collection from healthcare records only will continue for the duration of the trial, and all of the participant's data will be used in the trial analysis, including any data collected during follow-up prior to withdrawal of consent from follow-up schedule.

For f) and g), no further follow-up data will be collected past the point of withdrawal from follow-up schedule and from data collection from healthcare records, and data collected up to the point of withdrawal from follow-up schedule and from data collection from healthcare records will be used in the analysis.

In line with the principles for handling end of participation events in clinical trials research (PeRSEVERE) (https://ukcrc-ctu.org.uk/page-persevere/), a letter will be posted/emailed to the participant, thanking them for their involvement in the study, offering the opportunity to follow progress and outcomes of the study and requesting feedback on their reasons for withdrawing.

10.5.1 Eligibility violations

Participants who have been randomised but found to be ineligible after randomisation (and were actually ineligible at the time of randomisation) are **NOT** withdrawn from the study and continue with the protocol follow-up schedule. Continuation with the randomised treatment strategy will be at the discretion of the attending clinical team and participants may be withdrawn from the randomised treatment strategy but continue in the study (see Section 10.3). Eligibility violations will be recorded on the protocol deviation form and sent to CTRU.

Participants who were assessed as having a KC and are later found to require further surgery e.g. diagnosis of Melanoma, would be withdrawn from the study at the time of diagnosis and classified as a post-randomisation exclusion.

11. ASSESSMENTS/DATA COLLECTION

Randomisation, baseline assessments and follow-up weekly phone calls up to 26 weeks then monthly until healed, will be undertaken by a member of the clinical research team (eg clinician, clinical research nurse or RHCP. In-person SCSC visit will be at week 4 and a photograph will be taken at this visit.

When the participant indicates their wound has healed during the weekly/monthly phone calls, a confirmation of healing visit will be arranged. Ideally this will take place at the SCSC but this is not possible that a member of the clinical research team will visit the patient in a community wounds clinic or at home. Where an in-person visit with a member of the clinical research team is not possible, then a video call using NHS-approved technology with a photograph taken via screenshot can be submitted. In the unlikely event that neither an in-person visit nor a video call using NHS-approved technology cannot take place, then a photograph taken by the participant or participant's associate can be submitted to the local research team who will then send by Secure File Transfer to CTRU.

If the participant's wound is thought to be healed, they will be asked to remove all dressings and stop using compression prior to the confirmation visit. A blinded assessor (healthcare professional) will assess and photograph the wound and the participant will complete the modified Bluebelle WHQ. If, at the confirmation of healing visit, the wound is assessed as unhealed, a photograph will be taken and routine weekly/monthly phone calls and randomised treatment will be reinstated.

Medical record review will be undertaken at 26 and 52 weeks (if not healed at 26 weeks) to capture related SAEs (including hospitalisations for related infections) and date wound healed.

HRQoL (EQ-5D-5L) questionnaires will be completed face to face at baseline and week 4. Postal/electronic HRQoL and Health Care Resource Use questionnaires will be undertaken at 12 and 26 weeks and 52 weeks if unhealed. The modified Bluebelle WHQ will be undertaken at 4, 12, 26 and 52 weeks (until healing) and at the healing visit. Intervention acceptability questions will asked at week 4 and healing visit (intervention arm only). The POSAS questionnaire will be completed at the healing visit.

11.1 Submission of Trial Data

Where paper consent forms have been completed, a scanned copy of the Informed Consent Documents (ICDs) will be returned to the CTRU via the CTRU SFT system.

Randomisation data is submitted via the CTRU 24 hour randomisation system.
Participants will be given the choice of completing the quality of life and healthcare resource use questionnaires either on paper or electronically. For participants wishing to complete the questionnaires electronically they will be given the option of receiving an email or text message with a link to their questionnaire. Participants preferred method of questionnaire administration and completion will be collected during the consent process and applicable contact details, postal address/email address/mobile phone number, collected.. CTRU will send questionnaires to patients directly. Non-responders will receive reminders by the pre-stated preferred method of communication. The CTRU will contact sites at intervals throughout the study to ensure that consenting participant's contact details and status have not changed and that it is still appropriate to send them a questionnaire.

If a site becomes aware of a study participant experiencing a related and unexpected serious adverse event (RUSAE) as described in Section 12, a paper RUSAE CRF should be completed and a scanned copy sent to the CTRU within 24 hours of completion via the CTRU SFT system. If the site is using a Remote Data Entry (RDE) system the RUSAE can be entered directly. If site have not heard from CTRU within 24 hours of reporting an RUSAE then they must contact the CTRU to confirm receipt. Upon resolution of the event, in the case of paper reporting, the original wet-ink paper CRF should be posted to the CTRU and copy retained at site

Trial data recorded by site research staff and participants on paper CRFs will be submitted as original wet ink copies to the CTRU. All other data collection will be via RDE on electronic case report forms (eCRFs) will be managed by the CTRU.

Following receipt, the CTRU will contact trial sites to resolve any missing or discrepant data and any outstanding CRFs will be chased by CTRU until received or the data is confirmed as unavailable.

If a trial site is using paper records, it is their responsibility to maintain a file of essential trial documentation in the ISF, which will be provided by the CTRU. If the site is using RDE then backup or paper records will be as per local instructions.

11.2 Schedule of Events

Please see Table 2 on the next page.

Table 2. Summary of Assessments

Study Visit	Consent (can be on day of randomisation or before)	Pre randomisation	Randomisation/ post randomisation	Follow up assessments – until healing Weekly to 26 weeks then monthly +/- 3 days if weekly or +/- 7 days if monthly						Confirmation of healing
Week (post randomisation)	Pre-randomisation	Day 0		**1 - 26** Weekly phone FU till healing	**27- 52** Monthly phone FU till healing	**4** Clinic visit	**12** Postal/ electronic data collection	**26** Postal/ electronic data collection & record review	**52** Postal/ electronic data collection & record review	Ad hoc as required
STUDY VISIT WINDOW				+/-3 days	+/-7 days	+/-3 days	+/-3 days	+/-3 days	+/-7 days	Immediately after healing reported
Informed consent	X									
Wound area measurement (max length x max width) prior to any partial closure		X								
Wound area measurement (max length x max width) post partial closure (where applicable)		X								
Type of partial closure (if applicable)		X								
Eligibility for randomisation assessment CRF		X								
Demographics, medical history, & baseline clinical assessments		X								
EQ-5D-5L		X								
Randomisation			X							
Treatment strategy application			X			X				
AE/SAEs; Abx			X							
GP letter sent			X							
Issue participant ID card			X							

Healing status; AEs/SAEs; antibiotic use; treatment application and adherence				X	X	X				
Wound area measurement (max length x max width)						X				
Photograph of wound including scale with ruler						X				
Face-to-face questionnaires: Healthcare resource use, EQ-5D-5L, modified Bluebelle WHQ, intervention acceptability (CT only)						X[2]				
Postal/ electronic questionnaires: Healthcare resource use, EQ-5D-5L, modified Bluebelle WHQ							X	X	X[4]	
Related serious adverse events & healing (record review)								X	X[3]	
Face to face: Wound assessment; photography; POSAS; modified Bluebelle WHQ, confirmation of wound healing; Interention acceptability (CT only)										X[1]

[1] If wound assessed as unhealed, a photo is taken and weekly/monthly follow-up visits and treatment reinstated. When considered healed, patient to attend subsequent confirmation of healing and photograph. Assessment is by blinded assessor. If face-to-face is not possible then videocall, and if neither face-to-face nor videocall possible, then participant can submit their own photo.

[2] If patient does not attend 4 week in-person visit, questionnaires will need to be completed remotely

[3] Where applicable, if the wound is unhealed at 26 weeks

[4] Where applicable, if the wound is unhealed at 52 weeks

11.3 Eligibility and Baseline Assessments - Pre-Randomisation

The following will be collected on the Eligibility for Randomisation eCRF;

- Data relating to the clinical assessment of eligibility
- Formal confirmation of eligibility

For participants that complete formal eligibility to proceed to randomisation the following baseline data will be recorded prior to randomisation

- Demographic information
- Relevant medical history and clinical assessments
    - ABPI
    - CEAP
    - Factors affecting healing
    - Mobility
- Questionnaire
    - EQ-5D-5L

Baseline assessments and questionnaire pre-randomisation will be completed on the same day as surgery and randomisation.

11.4 Baseline Assessments - In Theatre

The following information will be collected in theatre immediately post-KC excision and prior to any dressing application using a sterile ruler (as per standard practice);

- Post excision wound measurement – length, width, depth (excision to fat/excision to fascia or periosteum)
- Type of partial closure (purse string suture, side-to-side partial closure e.g. with pulley sutures or buried sutures, none)
- Post partial closure measurement (where applicable) – length, width, depth (excision to fat/excision to fascia or periosteum)

11.5 Randomisation and Trial Intervention

Randomisation will be completed at the baseline visit by a member of the clinical research team after the baseline assessment, questionnaire and surgical excision have been completed. Wound area will be calculated by the 24-hour automated randomisation system using an elliptical method for stratification (see Section 9.4).

The following information will be recorded after randomisation and receiving the trial intervention;

- Participant trial ID number
- Randomisation allocation and details of intervention application
- Date
- Antibiotics
- Related Expected adverse and serious adverse events

11.6 Follow Up Assessments

Optimal care will continue throughout according to local practice. All participants will be followed up to a maximum of 52 weeks (+7days). Participants recruited during the final 6 months of the recruitment Phase will complete a minimum of 6 months follow-up.

Follow-up phone calls
Follow-up phone calls will be completed with participants until healing is confirmed weekly to 26 weeks and monthly thereafter to a maximum of 52 weeks post randomisation. The following information will be recorded:

- Wound status healed/unhealed
- Antibiotic use
- Treatment application and adherence
- Related expected/unexpected adverse and serious adverse events

Week 4 clinic visit*
The following information/assessments will be recorded:

- Wound assessment healed/unhealed
- Wound measurement
- Antibiotic use
- Treatment application and adherence
- Photography
- Related expected adverse and serious adverse events

- Questionnaires
    - Modified Bluebelle WHQ
    - EQ 5D 5L
    - Health Resource Use
    - Intervention acceptability (CT only)

*If the Week 4 clinic visit does not take place, a follow-up phone call will be made and questionnaires will be completed remotely.

Week 12 postal/electronic data collection
The following information will be recorded:

- Questionnaires
    - Modified Bluebelle WHQ
    - EQ 5D 5L
    - Health Resource Use

Week 26 postal/electronic data collection and record review
The following information will be recorded:

- Postal/electronic questionnaires
    - Modified Bluebelle WHQ
    - EQ 5D 5L
    - Health Resource Use
- Record review: a member of the research team will complete a review of the participant medical records and record the following information:
    - Related and expected serious adverse events
    - Date of healing (if applicable)

Week 52 record review (where not healed at Week 26)

- A member of the research team will complete a review of the participant medical records and record the following information *only for participants whose wounds had not healed by Week 26*:
    - Related and expected serious adverse events
    - Date of healing (if applicable)

Week 52 postal/electronic data collection (where applicable – only for participants with wounds remaining unhealed at Week 52)

- Postal/electronic questionnaires
    - Modified Bluebelle WHQ
    - EQ 5D 5L
    - Health Resource Use

11.7 Assessment of Healing

Healing is defined as complete epithelial cover in the absence of a scab, eschar or crust (adapted from Chetter *et al.* (20) and Arundel *et al.* (26)). Where participants indicate their wound has healed during a follow up phone call, a confirmation of healing visit will be arranged within 7 days. If the participant has been allocated to compression and is still using the intervention they will be asked to stop using compression prior to the visit to ensure compression markings are not visible in the photograph submitted for blinded central review (see Section 11.8). The following information/assessments will be recorded;

- Wound assessment healed/unhealed
- Photography
- Questionnaires
    - Modified Bluebell WHQ
    - POSAS
    - Intervention acceptability (CT only)

If the wound is assessed as unhealed, a photograph will be taken and submitted for blinded central review and the allocated treatment resumed and routine weekly/monthly phone calls re-instated.

11.8 Photography

Photography will be used for blinded validation of healing.

Participants will be asked for consent for photographs to be taken at the point of joining the study, this will be optional. However, participants may decline for a photograph to be taken at any time during the study and consent will be verbally reconfirmed prior to any photograph being taken. Photographs will be taken at the week 4 and confirmation of healing assessment visits.

A standard study camera (or suitable device) will be supplied to each site together with a work instruction detailing the use of a standardised photographic method including the use of a scale with ruler. For the purposes of consistency and interpretation of photographic data it is imperative that only the study camera/device supplied is used to take photographs. In addition, the work instruction will provide clear instructions on the anonymisation, secure transfer and deletion of the photographs (that is, there will be no local storage of photographs on the camera or NHS computer) to ensure standardisation across all centres.

All photographs will be submitted to CTRU via a secure electronic transfer system for central blinded photography review by clinical members of the Trial Management Group (TMG) who will not be aware of the participants identity, randomised intervention allocation or time point at which the photograph was taken.

11.9 Participant Questionnaires

Consent to complete questionnaires will be confirmed at the point of joining the study and is not optional. However, participants may decline to continue completing questionnaires at any time but remain in the study (see Section 10.5).

Baseline and week 4 questionnaires will be administered in clinic on paper/verbally.

Participants can choose their preferred method to receive follow up questionnaires (electronic/paper/verbal).

Participants will receive 1 reminder message via their preferred method if a completed questionnaire has not been received within the expected time frame (2 weeks for return by post and 1 week for electronic submissions).

EQ-5D-5L
EQ-5D-5L is an accepted, five-item, generic, health-related quality of life measure including 5 items that can be combined to provide a single assessment of utility of life in a particular for health state (27). The EQ-5D is a generic instrument (www.euroqol.org) and forms part of the National Institute for Health and Clinical Excellence (NICE) reference case for cost per QALY analysis.

EQ-5D-5L questionnaires will be completed at baseline, 4, 12 and 26 weeks and at week 52 (where applicable, if wound is not healed).

Health resource use

Health resource use questionnaires will be completed at 4, 12 and 26 (where applicable, if wound is not healed) and at week 52 (where applicable, if wound is not healed).

Modified Bluebelle Wound Healing Questionnaire (WHQ)
The modified Bluebelle WHQ(20) has been adapted from the original Bluebelle WHQ (28) for relevance for patients with open wounds by removing three items relating to spontaneous or deliberate wound dehiscence and use of dressings given these would not be relevant in this population. The time frame for the questionnaire has also been adapted to reflect the questionnaire should be completed since the participant had their open wound (at wound healing or since the last modified Bluebelle questionnaire was completed – Weeks 4, 12, 26 and 52 weeks (where applicable, if wound is not healed)) post randomisation and at healing, where applicable rather than the time since hospital discharge.

Intervention acceptability
Intervention acceptability will be explored through questions developed with PPI input to consider intervention comfort, convenience, and appearance. Details will be completed by participants in the intervention arm at week 4 and at the healing visit.

Patient and Observer Scar Assessment Scale (POSAS)
The POSAS (21) measures scar quality by evaluating visual, tactile, and sensory characteristics of the scar from the perspective of the observer and patients.

POSAS questionnaire will be completed at the confirmation of healing visit.

11.10 Definition of End of Trial

The end of the trial is defined as the date of the last data item for the last participant remaining in the trial.

12. SERIOUS ADVERSE EVENTS PROCEDURES

12.1 General Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or a clinical trial subject which does not necessarily have a causal relationship with the device/procedure.

A **Serious Adverse Event (SAE)** is an untoward occurrence that:
- Is fatal
- Is life threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the Investigator

A **Related Unexpected Serious Adverse Event (RUSAE)** means for an SAE occurring to a research participant in the opinion of the Chief Investigator was:
- 'Related' that is, it resulted from the administration of any of the research procedures, and
- 'Unexpected' that is, the type of event is not listed in the protocol as an expected occurrence.

Medical and scientific judgement must be exercised in deciding whether an event is serious (see Section 12.4 for Responsibilities). These characteristics/consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

12.2 Operational Definition for (S)AES

12.2.1 Expected (S)AEs – Not Reportable

This is a RCT in a patient population with high levels of morbidity and co-morbid diseases and as such in this patient population, new medical problems and deterioration of existing medical problems are expected.

In recognition of this, events fulfilling the definition of an AE or SAE will not be reported in this study unless they are classified as expected or 'related and unexpected'.

1. Expected and related trial treatment strategies and classified as an AE/SAEs (see Section 12.2.2)
2. Related to the trial treatment strategies and classified as a RUSAE (see Section 12.3)

12.2.2 Expected and Related AE/SAEs – Standard Reporting

The following AEs and SAEs are expected within the patient study population and will be reported from randomisation to trial completion on standard CRFs:

AEs:
- Randomised treatment strategy related adverse event e.g.
    - Compression related skin maceration/ excoriation/ dryness or other skin damage
    - Compression therapy related pain/discomfort
    - Compression related circulatory problems e.g. cyanosis/discoloured/ swollen toes, breathlessness, requiring immediate removal of the compression

SAEs:
- Hospital admission related to the surgical wound
- Hospital admission related to the trial treatment strategy (including cause)
- Death

As these events are expected within the study population they will not be subject to expedited reporting to the main Research Ethics Committee (REC).

12.3 Recording and Reporting SAEs and RUSAEs

Any study Related & Unexpected SAE (RUSAE) occurring will be recorded on a RUSAE Form, either entered directly on the database or recorded on paper and a scanned copy emailed by SFT to the CTRU **within 24 hours** of the Clinical/Research Team becoming aware of the event. All RUSAEs will be reviewed by the Chief Investigator and will be subject to expedited reporting to the Sponsor (dependent on Sponsor processes) and the main REC by the CTRU on behalf of the Chief Investigator within 15 days.

For each RUSAE the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to the investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the CTRU as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has been resolved or a final outcome has been reached. All RUSAEs will be reviewed by the Chief Investigator and will be subject to expedited reporting to the Sponsor and main REC by the CTRU on behalf of the Chief Investigator within 15 days.

12.4 Responsibilities

Principal Investigator (PI)/Authorised individual:

1. Checking for SAEs when participants attend for treatment / follow-up.
2. Judgement in assigning:
    - Seriousness
    - Relatedness
    - Expectedness
3. To ensure all RUSAEs are recorded and reported to the CTRU within 24 hours of becoming aware and to provide further follow-up information as soon as available.
4. To report RUSAEs to local committees in line with local arrangements.

Chief Investigator or Delegate:

- Assign relatedness and expected nature of SAEs where it has not been possible to obtain local assessment.
- Undertake SAE review.
- Review all events assessed as Related / Unexpected in the opinion of the local investigator. In the event of disagreement between local assessment and the Chief Investigator, local assessment may be upgraded or downgraded by the Chief Investigator prior to reporting to the main REC.

CTRU:

- Expedited reporting of Related / Unexpected SAEs to the main REC and Sponsor within required timelines.
- Preparing annual safety reports to main REC and periodic safety reports to TSC and DMEC as appropriate.
- Notifying Investigators of Related / Unexpected SAEs which compromise participant safety.

TSC:

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

DMEC:
In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

13. ECONOMIC EVALUATION

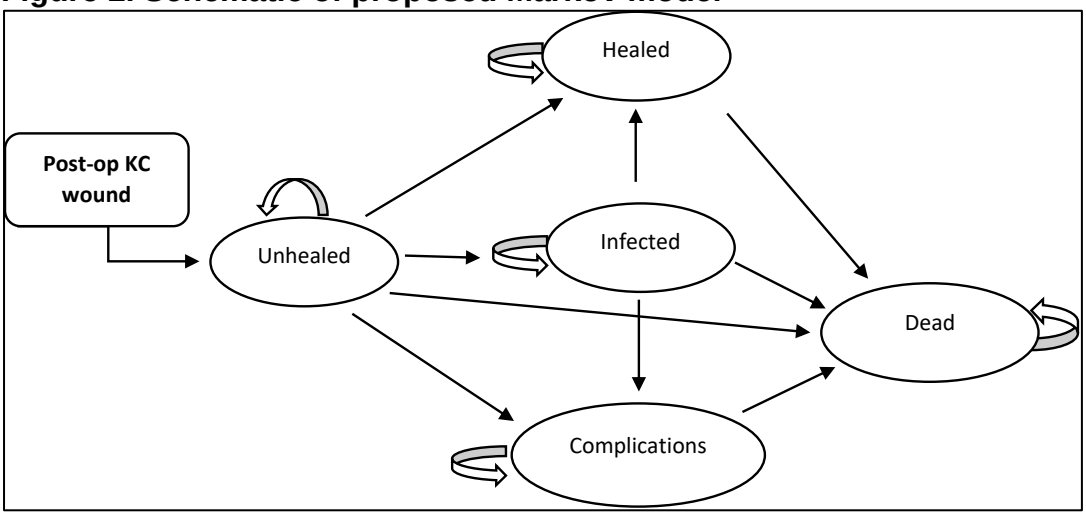
The economic evaluation will assess the cost-effectiveness of CT plus SC versus SC alone using within-trial analysis and a Decision Analytic Model (DAM) to assess the argument over a longer time perspective.

The within-trial-based economic evaluation will be undertaken for the 52 week period of the trial. The proposed methods for the economic evaluation follow the reference case set out by NICE(29). Results will be presented according to the new updated international CHEERS statement (22).

The DAM will be developed over the course of the project but will first be evaluated at 52 weeks. This will help in assessing alignment with and validation by the within-trial analysis and provide some insight on cost-effectiveness drivers.

The DAM will most likely be based on a Markov model with states based on healed, unhealed, infected and dead. A schematic of this model is shown in Figure 2 below and is based on insight from the HEALS feasibility study, available literature and assumptions about leg wounds.

Figure 2. Schematic of proposed Markov model



The infected health state may affect the trajectory of wound healing as observed in the HEALS feasibility study where 30.2% of post-operative KC patients experience delayed wound healing. As observed with chronic wounds, the presence of infection can increase the costs of management, adversely affect patient HRQoL and also increase the risk of co-morbidities. The final choice of health states will be informed by discussions with the clinical team and further insights from literature. Collaboration will occur with the statistical analysis team to determine whether more nuanced definitions of unhealed wounds can be supported and to add insight. The statistical and health economics analysis will also explore the optimal approach to estimating expected healing times of those censored observations (conventionally done with parametric survival models).

A targeted review of literature to inform model structure, inputs and assumptions will be carried out prior to conducting the DAM.

Perspective and time horizon
Costs will be assessed from an NHS and Personal Social Services (PSS) perspective. Additional personal costs will be collected for a wider societal perspective. Costs and outcomes will be calculated for the trial follow-up period of 52 weeks for the within-trial analysis. The DAM will first be evaluated at 52 weeks and take a time horizon based on validation by clinicians and the literature.

Measures of effectiveness
Outcomes will be measured in QALYs. Participants' responses to the EQ-5D-5L questionnaire at Baseline, Weeks 4, 12, 26 and 52, will be converted to HRQoL scores using the standard UK general population time-trade off tariff values (29). The resulting QALYs will be constructed using the current Crosswalk Index Valuation set as currently recommended by NICE(30) or any equivalent update to that advice.

Analysis of HRQoL
A multivariate longitudinal regression model will be fit to estimate the incremental impact of treatment over time. Random Effects will be used to capture patient and potentially centre heterogeneity. 95% confidence intervals will be reported and the variance – covariance matrix will be used to inform the economic evaluation Probabilistic Sensitivity Analyses. An additional related analysis will look at the impact of healing on EQ-5D-5L responses taking into account underlying patient heterogeneity. This secondary analysis will be used to inform HRQoL values in a state-dependent Markov model.

Measures of resource use
The health care resource use questionnaire will collect information on NHS and personal social care use in line with NICE guidelines (29). Health care resource will include primary, tertiary and secondary care use including hospital visits, community nurse visits, GP practice visits and community prescribing. Unit costs from PSSRU and Reference Costs will be attached to resource use reflecting costs to the NHS.

Treatment costs
The costs of SC post-op care and wound management will be estimated and will include clinic visits, dressings provided through self-care, SCSC clinical team, practice nurses for mobile patients/district nurses for immobile patients), additional advice (see 10.1) . The cost of CT will be estimated, the choice of which will be based on general consensus of type(s) used which reflect clinical practice.

Incremental Cost-Effectiveness Ratio (ICER) and Net incremental monetary/health benefit
Results will be presented in standard formats such as the ICER, i.e. costs per QALYs and Incremental Net Benefits (health & monetary) and assessed at cost-effectiveness thresholds relevant of the UK. NICE considers a cost per QALY within the range of £20,000-£30,000 to be acceptable (29).

Dealing with missing data
The approach to missing data will follow good practice guidelines for cost effectiveness analysis alongside clinical trials (31). Indeed, analytical techniques will be jointly determined with the statistical co-applicants to ensure consistency across the project (e.g., multiple imputation techniques).

Sensitivity analyses
Uncertainty will be explored using univariate and Probabilistic Sensitivity Analysis and presented in Cost-Effective Acceptability Curves (CEACs).

Equity considerations
We will also adopt principles of Distributional Cost-Effectiveness Analysis to explore equity as well as efficiency considerations.

14. ENDPOINTS

Primary endpoint measure

The primary outcome is ***time to complete healing (epithelialisation) of the surgical wound*** from randomisation to the date the wound is confirmed as healed. Participants will be asked at routine

weekly/monthly phone calls whether the wound has completely healed, and if affirmative, when this was observed. A healing confirmation visit will be arranged (see Section 11.7) for confirmation of wound healing assessment with a blinded clinical assessor and the healed wound area on the leg photographed for blind central review. After confirmation of healing, the date of complete healing will be taken as the date that healing is first reported.

Healing is defined as complete epithelial cover in the absence of a scab, eschar or crust (adapted from Chetter *et al.* (20) and Arundel *et al.* (26)).

Where participants have completed full 52-week post randomisation follow-up, wounds that have not been confirmed healed will be censored at 52 weeks for purposes of analysis. Where participants are lost to follow-up or withdraw before wound healing confirmed and before week 52, wounds will be censored at the date of last known follow-up assessment/clinic visit/participant contact with wound remaining unhealed.

Secondary endpoint measures

Antibiotic use: measured by number of days participant prescribed antibiotics for the wound.

Wound infection: measured by modified Bluebelle Wound Healing Questionnaire (WHQ) score. The modified Bluebelle WHQ is a 15-item patient-reported measure including an ordinal scale to capture symptom severity ('not at all'=0, 'a little'=1, 'quite a bit'=2, 'a lot'=3) and a binary scale for wound care intervention items ('yes'=1, 'no'=0). Total score is calculated by summing the individual question scores. The modified Bluebelle WHQ is currently being validated by the SWHSI-2 trial team (32)

Safety: measured by frequencies of related adverse/serious adverse events including complications/hospitalisations

Scar Quality: POSAS measures scar quality by evaluating visual, tactile, and sensory characteristics of the scar from the perspective of the observer and patients. Each item is rated on a 10-point score. The lowest score is 1 which corresponds to the situation of normal skin. Score 10 indicates the largest difference from normal skin. The total score of both patient and observer scales is calculated by summing the scores of the items.

Intervention acceptability and treatment adherence: elicited information will include use of unplanned compression (in the SC arm) and reported day/night frequency of compression wear in the compression arm and reasons for discontinuation.

Wound area percentage reduction: percentage reduction from baseline at Week 4 post surgery will be calculated.

Health-related quality of life (HRQoL): using EQ-5D-5L questionnaire responses and the current Crosswalk Index Valuation set as currently recommended by NICE(30) or any equivalent update to that advice, to derive QALYs.

Health Care resource use: will include primary, tertiary and secondary care use including hospital visits, community nurse visits, GP practice visits and community prescribing. Unit costs from PSSRU and Reference Costs will be attached to resource use reflecting costs to the NHS. Additional personal costs will be collected for a wider societal perspective.

Exploratory endpoint measure
Intervention acceptability will be explored through questions developed with PPI input to consider intervention comfort, convenience, and appearance.

15. STATISTICAL CONSIDERATIONS

The sample size estimates are based upon our HEALS feasibility cohort and clinical and health economic considerations regarding an important reduction in number of days until complete healing. Assuming a median time to healing of 81 days in the SC arm(12) a total of 396 randomised participants (198 per group) will provide 90% power for detecting a target effect size of 30% reduction in time to healing in the CT group (57 days, HR =1.43), 2-sided log-rank test at 5% significance level and 10% attrition.

16. STATISTICAL ANALYSIS

The statistical analysis will follow a predetermined, approved, version-controlled statistical analysis plan (SAP), and reporting will be in line with Consolidated Standards Of Reporting Trials (CONSORT) standards. Statistical monitoring of safety data and underlying assumptions of the statistical design will be conducted and reported to the DMEC according to an agreed DMEC Charter.

Baseline demographic data will be summarised to assess comparability between treatment arms using means and standard deviations or medians and interquartile ranges as appropriate for continuous variables, and numbers and percentages for binary and categorical variables. These same methods will be used to generate descriptive statistics where required.

Primary analysis of primary outcome measure
Primary analysis of the primary outcome measure, time to complete healing will be conducted on the modified* intention-to-treat (ITT) population using a multivariable Cox Proportional Hazards (PH) regression model adjusted for the minimisation factors post-excision wound area and wound depth; centre will be explored as a random effect. Estimated HR will be presented with 95% CI and significance. Unadjusted Kaplan-Meier plots and estimates of survival functions (where 'survival' corresponds to healing not observed) and the stratified log-rank test statistic and its significance will be also reported. Should the PH assumption appear to be violated, an appropriate alternative analysis method will be used.

*The modified ITT population consists of all participants analysed according to their randomised allocation with the exception of any participants found ineligible post-randomisation due to a requirement for further surgery e.g. the identification of melanoma. In the rare event that this occurs, these participants will be pre-emptively withdrawn from further trial participation due to ethical concerns around the complex patient pathway and potential patient distress during follow-up. We can confirm this would not introduce bias into the estimate of the treatment effect.

Sensitivity analyses
Death as a competing risk: Should incidence of death be substantial as a competing risk event, a multivariable Fine & Gray(33) regression model adjusted for the minimisation factors may be fitted to the primary outcome measure.
Treatment adherence: Patterns of treatment adherence will be explored, and an appropriate statistical method taking adherence into account while respecting the randomisation (e.g. rank preserving structural or structural nested failure time model (34-36), or marginal structural model (37, 38)) will be used to model causal treatment effect for observed adherence.
Alignment with Health Economic analysis: A parametric model consistent with that which is required in the health economic analyses for providing transition probabilities beyond the time frame of the trial will be fitted to the primary outcome measure.

Analysis of secondary outcome measures
Wound infection measured by modified Bluebelle (WHQ) a multivariable, random coefficients, repeated measures linear regression model will be fitted to modified Bluebelle WHQ score over time (until complete wound healing), including minimisation factors and randomised treatment. Centre, participant, and participant-by-time interaction random effects will be explored. Time, treatment, and treatment-by-time

interaction will be fitted as fixed effects. An estimate for the magnitude of the treatment-by-time interaction and corresponding 2-sided 95% CI will be reported.

Number of days prescribed antibiotics for infection of the wound: a multivariable Poisson regression model will be fitted to whether participant has been prescribed antibiotics over time, with an offset term for time at risk of being on antibiotics, including the minimisation factors and randomised treatment. Centre and participant random effects will be explored. An estimate for the difference in number of days where antibiotic prescribed 95% confidence interval will be reported.

Scar Quality (POSAS): A multivariable linear regression model will be fitted to both participant and clinician POSAS scores, including the minimisation factors and randomised treatment. Centre random effects will be explored. Estimates for the differences in POSAS scores between the CT and SC arms and 95% confidence intervals will be reported.

Safety: events including related complications and hospitalisations to healing (max 52 weeks post randomisation) will be summarised descriptively by treatment received.

Associations between partial closure method, post partial closure wound area, and time to healing: *Partial wound closure method and post partial closure wound area* will be included as additional covariates in the primary endpoint analysis model (multivariable Cox PH model).

Exploratory analyses

Development of a predictive marker of healing: a multivariable model to predict time to complete wound healing incorporating the minimisation factors and Week 4 measurements of reduction in wound area from baseline will be developed in line with the Prognosis Research Strategy (PROGRESS) initiative (39-42).

Intervention acceptability and treatment adherence: both will be summarised descriptively overall, and treatment adherence will also be summarised by randomised treatment group.

17. TRIAL MONITORING

A Trial Monitoring Plan (TMP) will be developed and agreed by the TMG and TSC based on the trial risk assessment; this may include on site monitoring.

An independent DMEC will review the safety and ethics of the study. Detailed unblinded reports will be prepared by the CTRU for the DMEC at regular intervals. The DMEC will be provided with detailed unblinded reports containing the information agreed in the data monitoring analysis plan.

18. TRIAL STEERING COMMITTEE and/or DATA MONITORING AND ETHICS COMMITTEE

A TMP will be developed and agreed by the TMG and TSC based on the trial risk assessment; this may include on site monitoring.

18.1 Data Monitoring

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. However missing data items will not be chased from participants (although missing questionnaires sometimes are). The [**CTRU/Sponsor**] will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the [**CTRU/Sponsor**]. Source data verification will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

18.2 Clinical Governance Issues

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual NHS Trusts.

19. QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

19.1 Quality Assurance

The trial will be conducted in accordance with the principle of GCP in clinical trials as detailed by the Medical Research Council (MRC), the NHS Research Governance Framework (RGF) and Scottish Executive Health Department RGF for Health and Social Care 2006, and through adherence to CTRU Standard Operating Procedures (SOPs).

19.2 Serious Breaches

Investigators are required to promptly notify the CTRU of a serious breach (as defined in the latest version of the National Research Ethics Service (NRES) SOP). A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards for conduct of non-Clinical Trial of an Investigational Medicinal Products (non-CTIMPs)) which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research. In the event of doubt or for further information, the Investigator should contact the Senior Trial Co-ordinator at the CTRU.

19.3 Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland (1996 or later). Informed written/witnessed verbal consent will be obtained from the patients prior to randomisation into the study. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. The study will be submitted to and approved by a main REC and the appropriate site specific assessor for each participating centre prior to entering patients into the study. The CTRU will provide the main REC with a copy of the final protocol, PIS, consent forms and all other relevant study documentation.

20. CONFIDENTIALITY

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CTRU. The CTRU will comply with all aspects of the 2018 Data Protection Act and operationally this will include:

- consent from participants to record personal details including name*, date of birth*, address and telephone number, email address, NHS number, hospital number, GP name and address
- appropriate storage, restricted access and disposal arrangements for participant personal and clinical details
- consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation.

- consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- participant name, address, email address and telephone number will be collected when a participant is randomised into the trial but all other data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two participant identifiers, usually the participant's initials and date of birth.
- where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the participant's name must be obliterated by site before sending.
- where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

If a participant withdraws consent from further trial treatment and / or further collection of data their data will remain on file and will be included in the final study analysis.

20.1 Archiving

At the end of the trial, data will be securely archived in line with the Sponsor's procedures for a minimum of 5 years. Data held by the CTRU will be archived in the Leeds Sponsor archive facility and site data and documents will be archived at site. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

21. STATEMENT OF INDEMNITY

This trial is sponsored by the University of Leeds and the University of Leeds will be liable for negligent harm caused by the design of the trial. The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial and the NHS remains liable for clinical negligence and other negligent harm to patients under this duty of care. The sponsor has not made any arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises.

22. STUDY ORGANISATIONAL STRUCTURE

22.1 Individuals and Individual Organisations

Trial Sponsor: In accordance with the UK Policy Framework for Health and Social Care Research, the Sponsor of the study is the University of Leeds. Responsibilities for conduct are delegated as below.

Chief Investigator: as defined by the NHS RGF, is responsible for the design, management and reporting of the trial. The Chief Investigator will be responsible for the day to day running of the trial including obtaining Health Research Authority (HRA) and local site approvals, clinical set-up, ongoing management including training, monitoring reports and promotion of the trial.

Clinical Trials Research Unit (CTRU): The CTRU will have responsibility for data management and analysis in accordance with the RGF. The CTRU will provide data management according to applicable CTRU SOPs, including, randomisation design and service, database development and provision, protocol review, trial design, and statistical analysis for the trial.

HEALS2 Clinical Research Practitioner (CRP): The CRPs based at recruiting sites will be responsible for the day-to-day management of the trial, patient recruitment, obtaining informed consent, randomisation, liaison with medical staff, CRF completion and annual follow-up assessments.

22.2 Oversight/Trial Monitoring Groups

22.2.1 Trial Management Group (TMG)

The TMG, comprising the Chief Investigotor, CTRU team and co-applicants will be assigned responsibility for the clinical set up, ongoing management, promotion of the trial, and for the interpretation and publishing of the results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (III) obtaining approval from the Main REC and supporting applications for Site Specific Assessments, (iv) completing cost estimates on project initiation, (v) nominating members and facilitating the TSC and DMEC, (vi) reporting of SAEs, (vii) monitor of screening, recruitment, treatment and follow up procedures, (viii) auditing consent procedures, data collection, trial end point validation and database development and (viv) central review of photographs.

22.2.2 Trial Steering Committee (TSC)

The TSC, with an independent chair, will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an independent chair, not less than two other independent members and a consumer representative (PPI). The Chief Investigator and other members of the TMG may attend the TSC meetings and present and report progress. The Committee will meet 6 monthly.

22.2.3 Data Monitoring and Ethics Committee (DMEC)

The DMEC will include independent membership and will review the safety and ethics of the trial by reviewing interim data during recruitment. The Committee will meet annually as a minimum.

23. PUBLICATION POLICY

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to the start of recruitment.

The success of the trial depends upon collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- Conception and design, or acquisition of data or analysis and interpretation of data,
- Drafting the article or revising it critically for important intellectual content,
- And final approval of the version to be published,
- And that all these conditions must be met (www.icmje.org)

For core publications, co-applicants and members of the CTRU trial team will be given the opportunity to contribute to drafting and reviewing manuscripts; those who contribute as per the ICMJE guidance will be named authors on publications. For methodology papers, authorship will be discussed with the TMG and an authorship sub-team agreed.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the TSC. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

24. REFERENCES

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25. ADDITIONAL INFORMATION/APPENDICES

25.1 APPENDIX 1: Clinical Etiology Anatomy Pathophysiology (CEAP) Classification (24)

It is outwith the scope of this study to perform a full venous assessment. The trial will therefore only utilise a modification of the clinical component of the CEAP.

C class	Description
C0	No visible or palpable signs of venous disease
C1	Telangiectasias or reticular veins
C2	Varicose veins
C3	Oedema
C4	Changes in skin and subcutaneous tissue secondary to chronic venous disease (CVD) e.g. Pigmentation, varicose eczema, lipodermatosclerosis or atrophie blanche
C5	Healed, previous venous ulcer
C6	Active venous ulcer

25.2 APPENDIX 2: List of Amendments