CUPRA trial

North Cumbria Integrated Care NHS Foundation Trust

Prospective, randomised controlled trial assessing MedCu copper dressing for lower limb ulcer management

(CUPRA trial, Copper dressings for Ulcers; Prospective Randomised Appraisal)

Version 1.0, dd 18 October 2024

Chief Investigator's Statement of Ownership and Content.

I, Jane Todhunter, confirm that this protocol is my work and is owned by me. The protocol conforms with standards outlined in the Declaration of Helsinki 1964.

Name (PRINT):___Jane Todhunter_____

Signature:_____

Date: _____

RESEARCH PROTOCOL SUMMARY

TITLE:	**Prospective, randomised controlled trial assessing MedCu copper dressing for lower limb management** **(CUPRA trial, Copper dressings for lower limb Ulcers; Prospective Randomised Appraisal)**
Short title:	CUPRA trial
IRAS ethics number	350241
ISRCTN trial number	To be confirmed
Device description	CE-marked wound dressing: MedCu (by MedCu Technologies) dressings are impregnated with copper oxide microparticles. MedCu dressings are single-use wound dressing with an internal absorbent layer and one or two external non-woven, non-adherent layers.
Study design	Prospective, randomised controlled trial
Primary objective	To determine the relative efficacy and safety of MedCu copper-impregnated dressing versus standard of care for the management of lower limb ulcers, measured through wound status (healed vs non-healed) at 12 weeks post-baseline.
Secondary objectives	To determine the wider efficacy and safety of MedCu copper-impregnated dressing for the management of lower limb ulcers at 4, 8 and 12 weeks post-baseline - Any adverse events related to the use of allocated dressings, and rates of (patient-requested) discontinuation of dressing. - Wound status (healed vs non-healed) - Quality of Life (EQ-5D-5L) - Lower limb symptoms (VEINES Sym) - Types of dressings applied in standard care arm
Patient population	First known randomised controlled trial of MedCu dressing. Therefore pragmatic approach to allow inclusion of wider cohort of patients. Patients with lower limb ulcer of any underlying aetiology are considered for inclusion. Index wound size should be minimum of $1cm^2$ and can be maximum of $30cm^2$ (only one index wound per patient to be included in study). Stratification for wound size at randomisation stage.

	Participants must not be palliative and have the mental and physical capacity to provide informed written consent and complete patient reported outcome measures. Participants are recruited from the local hospital / community clinics.
Sample size	The primary outcome, wound status (healed vs non-healed) is used for sample size calculation. Treatment will be random and 1:1 allocation: n = 33 standard of care and n = 33 MedCu copper dressing cases, giving a combined total of **n = 66** participants. The sample size calculation is based on 2x2 Chi-squared test (80% power and 5% alpha). The hypothesis is a minimum 20% (effect size 0.40) difference in wound healed at week 12, with then allocation for 30% withdrawal/dropout rate added. Option to expand sample size, subject to review of safety data, after initial sample size has been reached. This then allows wound healing comparison for purer sample of 'leg ulcers' and 'foot ulcers' separately from each other. For each of these sub-samples, 66 participants are to be recruited.
Sponsor	North Cumbria Integrated Care NHS Foundation Trust
Funder	Creed Health Unit 2, Hamilton Court, Oakham Business Park, Mansfield, Notts. NG18 5FB, UK Tel: +44 (0) 1623 391578 Email: sales@creedhealth.co.uk E: leo.fielding@creedhealth.co.uk W: https://www.creedhealth.co.uk/
Chief Investigator	Jane Todhunter, vascular specialist nurse, Vascular Surgery Dept, North Cumbria University Hospitals NHS Trust, Cumberland Infirmary, Carlisle, CA2 7HY Jane.todhunter@ncuh.nhs.uk
Co-investigators	Dr Leon Jonker PhD, Research Project Lead, Tel. 01228608926; Cumbria Partnership NHS Foundation Trust R&D Department, Cumberland Infirmary, Carlisle, CA2 7HY Leon.jonker@cumbria.nhs.uk Grace Messenger, Head of Podiatry, North Cumbria Integrated Care NHS Foundation Trust, Cumberland Infirmary, Carlisle, CA2 7HY , grace.messenger@ncic.nhs.uk

Organisations where research will take place	North Cumbria Integrated Care NHS Foundation Trust Cumberland Infirmary, Newtown Road Carlisle, CA2 7HY Optional: up to 2 other NHS Trusts, exact sites to be determined (once trial has been listed on National Institute for Health Research National Portfolio) – amendment to be submitted to HRA once additional site identified.
Planned timeline	First patient, first visit: 1Mar2025, Last patient, first visit: 31Apr2026 Last patient, last visit: 30Jul2026 Trial end date: 30Sep2026
Protocol version, date	Version 1.0, 18Oct2024

TABLE OF CONTENTS

1. LAY SUMMARY

Prompt appropriate treatment to heal lower limb ulcers is desirable to reduce the risk of complications (infection or even amputation) and to minimise the considerable costs involved in caring for chronic wounds. To date, clinicians have usually been guided by clinical signs (presence of redness, puss, bad odour) to determine if a wound is infected and may need antimicrobial dressings applied. However, there is limited evidence whether proactive antimicrobial dressing treatment may minimise the risk of wounds becoming infected, and if this approach may help accelerate wound healing. This present study will aim to determine if treatment of lower limb ulcers with a copper-oxide particle impregnated dressing (called MedCu, or 'copper dressing') can aid in wound healing of lower limb ulcers compared to standard care dressings. Copper is a known antimicrobial agent and there is early evidence that in parallel it can also help to accelerate wound healing. A minimum total of 66 patients with a lower limb (leg / foot) ulcer will be enrolled in this study, and allocated 1:1 to either standard care or the copper dressing. After a treatment period of up to 12 weeks, wound healing in the two groups will be compared to see if healing rates differ.

2. INTRODUCTION

Health and financial burden of ulcers

Chronic ulcers are associated with considerable expense, morbidity and impaired quality of life (Graves et al, 2022; Guest et al, 2020). The natural history and pathophysiology of lower extremity (foot and leg) wounds – particularly in those patients who have venous insufficiency and or other chronic disease affecting the vasculature such as diabetes and peripheral arterial disease - is a continuous cycle of healing and breakdown over years and sometimes decades (Raffetto et al, 2020). A positive relationship has been observed between eg venous leg ulcer occurrence and specific modern lifestyle risk factors such as sedentary lifestyles and obesity (Brand *et al* 1998). Bacterial infection of wounds carries the risk of further degenerative complications including cellulitis, necrotising fasciitis, and sepsis Grothier & Stephenson, 2015). It has long been recognised that an additional undesirable effect of wound infection is that it delays, or even stops altogether, the wound healing process (Raffetto et al, 2020, Halbert et al, 1992).

Copper and wounds

There is evidence that copper has unique properties in relation to wounds. It has been shown to 1) promote angiogenesis and 2) exert antimicrobial effects. In relation to the first point, various wound healing and repair mechanisms interplay with copper (Kornblatt et al, 2016).

Copper can stimulate angiogenesis, the formation of new blood vessels, by inducing generation of growth factors such as VEGF during the initial inflammatory response in a wound, and it also promotes subsequent cell migration and production of 'scaffolding' proteins such as collagens and elastin fibres in the proliferation and remodelling phases of wound healing (Gerard et al, 2010; Sen et al, 2002). This positive copper-derived effect on

wound healing has been demonstrated in wound animal models, and conversely copper inhibition delays wound closure (Kumar et al, 2020).

The antimicrobial effect of copper has been recognised and utilised for centuries. More recent research has elucidated in more detail the efficacy and mechanism of action for copper's antimicrobial activity against microorganisms (including bacteria). Though it can negatively impact microorganisms in different ways, the route of bactericidal activity is the the generation of reactive oxygen species, which irreversibly damages membranes and leads to breakdown of bacterial proteins, lipids and DNA (Salah et al , 2021; Borkow & Gabbay, 2005). Copper oxide impregnated wound dressings, possess potent antimicrobial properties. MedCu is one manufacturer of such dressings, and the devices have regulatory approval in place in a number of regions (USA, EU, UK) for use in treatment of acute and chronic wounds, such as diabetic ulcers, pressure injuries, and venous ulcers. These single use sterile wound dressings incorporate a highly absorbent layer and one or two nonbinding layers. All layers are impregnated with copper oxide microparticles, allowing continuous slow release of copper ions at very low concentrations (Borkow et al, 2022).

Real-world application of MedCu copper dressing

Initial findings of the efficacy of MedCu copper oxide dressings have been publish in recent years. One paper outlined the case of a hard-to-heal diabetic foot ulcer (DFU) and how MedCu dressing reduced the bioburden in the wound, as measured by fluorescence imaging, before wound closure was achieved (Lu et al, 2022). In a case series of four patients with mainly amputation-related wounds, uneventful healing was observed when MedCu dressing was applied (Melamed and Borkow, 2023). Unlike silver dressing, which should not be applied continuously for more than a few weeks, in these cases the MedCu copper dressing could be and were applied throughout. Wound healing, including that of lower limb ulcers, was also achieved in a large portion of patients when initial silver dressing was replaced with MedCu copper dressing (Gorel et al, 2024). Limitations of that study were the wider variation in wound aetiologies and the single arm approach without comparison to either standard care, continuation of silver dressing, or initial copper-based dressing treatment followed by silver. Similar results were obtained in a 13-patient cohort of diabetic foot ulcer patients (Melamed et al, 2021).

With this study, a real-world approach is taken to assess if MedCu copper dressing can aid in promoting wound healing when compared to standard of care. This also presents an opportunity to appraise the safety profile of copper dressing for use on lower limb ulcers.

3. STUDY HYPOTHESIS

3.1 Primary objective

To determine the efficacy of MedCu copper oxide impregnated wound dressing for the management of lower limb ulcers, measured through wound status (healed vs non-healed) at 12 weeks post-baseline

3.2 Secondary objective

To determine the efficacy and safety of MedCu copper oxide impregnated wound dressing for the management of lower limb ulcers at 4, 8 and 12 weeks post-baseline

- Wound status (healed vs non-healed at 4 and 8 weeks)
- Healing rate (ulcer size, PUSH score)
- Generic quality of Life (EQ-5D-5L)
- Lower limb symptoms (VEINES Sym)

4. STUDY PROTOCOL

4.1 Study design and timeline

This concerns a prospective randomized controlled trial. The study will be carried out by North Cumbria Integrated Care NHS trust. Up to two other NHS Trusts will be considered for inclusion in the trial as recruitment sites once the trial has been listed on the National Institute for Health Research national portfolio. The study will take place in local community and hospital settings with support and oversight from research staff. Research delivery staff will be delegated to provide support with data collection and processing.

Table 2. Anticipated timeline

Month	Setup	Recruitment	Analysis	Finalise
Jan-25	Submission for HRA approval			
Feb-25	NIHR portfolio adoption			
Mar-25	HRA and Trust approval	Start recruitment; first patient, first visit		
Apr-26		Finish recruitment		
Jul-26		Last participant, last visit		
Aug-26			Analyze data	
Sep-26				Finalise analysis & report

4.2 Participant identification & screening

Patients who are referred to the local clinical team with a lower limb ulcer will be screened for eligibility for this study by the direct care team. The research team will then be informed on potential participants and the patient information sheet will be added to the appointment letter. All eligible patients will be invited to take part until the required numbers have been achieved. Patients

will be recruited sequentially and be allocated into one of two randomisation groups. The eligible patient population is defined in the Inclusion and Exclusion criteria section.

There may be occasions where the consent may be delegated to a member of the research team; this is an option as long as the patients has given verbal consent for this when asked by the direct care team first. During the first appointment, the study will be discussed in further detail and the participant has the opportunity to ask questions that they may have. If potential participants meet the eligibility criteria, the patients can be consented by the direct care team personnel or this may be delegated to the research delivery team (again, as long as the patient's verbal consent has been sought for the latter arrangement). A screening form will be completed for potentially eligible patients to confirm that they indeed meet the trial criteria.

Participants will receive no incentives and consent will be regarded as a process and not a one off event. Participants are free to withdraw from the study at any time without the need to give any reasons for withdrawal. Their standard care will not be affected by either declining to participate in the study or withdrawing during participation – patients would still be managed with an approved type of wound dressing even if not in the trial.

4.3 Recruitment

Participants will be allocated to one of two randomisation arms. Patients in both arms will be given standard supportive advice on lower limb ulcers, to include compression bandaging, and their general management.

All participants will have demographic data obtained and the following measures (table 3):

Table 3. Baseline measures

Weeks	0	2	4	6#	8	10	12#
Baseline measures (demographics, medical history, vascular history)	X						
Ulcer wound status + dressing use status	X		X		X		X
Ulcer size, digitally measured with Healthy io App	X		X		X		X
PUSH score	X		X		X		X
EQ-5D-5L	X						X
VEINES Sym	X		X		X		X
Photo of ulcer (or original index site); subject to additional consent by patient (recorded with Healthy io App)	X		X		X		X

 # Allowed to be up to 2 weeks early or late. For all follow-up dates, calculation is based on original enrolment date for patient, even if deviation for one or more follow-up timepoints.

The Pressure Ulcer Scale for Healing (PUSH) tool, see Appendix 1 is a standardised method of assessing and monitoring the severity and healing of both pressure ulcers and venous leg ulcers (Stotts et al, 2001; Ratliff & Rodeheaver 2005). Concerns have been raised regarding the criterion

validity and intra-rater reliability of the tool (Pillen et al 2009) however in the absence of other valid tools it provides a comprehensive parallel assessment of the ulcer along with measuring size alone.

VEINES-Symptoms is a patient reported outcome measure score that focuses on lower limb health, and can be used in patients both with, or without a lower limb ulcer (Launois 2015)

During the recruitment process the research team acts as a contact point and coordinator for patients requiring information and support. If concerns are raised on participants (mental) wellbeing based on the home visits or outcome of the assessments, referral of patients/families on to other professional agencies will be done as appropriate and according to the Trust guideline.

4.4 Follow-up and Standard care

Patients are in the study for the planned 12 weeks, even if the index lower limb ulcer has healed prior to that time point. Apart from the specific research measurements and assessments, the patient will be followed up as they would in normal clinical practice. The vascular or community nurse will redress the lower limb ulcer as per allocated dressing choice, and will conduct the measurement of the lower limb ulcer (Healthy io App and PUSH score). The researcher will visit the patient at baseline (week 0), week 4 , week 8 and week 12 of study participation to randomise the patient and conduct the questionnaires.

Patients identified in the community (primary care, podiatry, or non-vascular surgery dept) can be invited to participate in the study via the vascular surgery department.

Standard wound care will be provided throughout the trial period, as well as meeting any other medical needs that arise. The SIGN guidelines for leg ulcer care form the framework for management of the leg ulcers (https://www.sign.ac.uk/media/1058/sign120.pdf), and the NICE guildelines form the framework for the most common foot ulcer type, diabetic foot ulcers (https://www.nice.org.uk/guidance/ng19)

4.5 Outcome measures

4.5.1 Primary outcome measures

Wound status (healed vs non-healed)

In line with the definition used by the VenUS6 research trial team, the primary outcome of this trial is time to healing of the reference ulcer, and the definition is: complete epithelial cover in the absence of a scab (eschar) with no dressing required. There is no minimum length of time that the index site has to have been in said condition for when participant present for follow-up study visit.

4.5.2 Secondary outcome measures

Clinical outcome measures

- ulcer size, measured digitally with Healthy io App
- Size and characteristics of ulcer, determined with PUSH score
- Quality of life score, determined with EQ-5D-5L score.
- Patient discomfort related to legs, VEINES Sym questionnaire

- Patient withdrawal rates due to change in management (e.g. need for surgery)
- Lower limb ulcer infection rates
- Types of dressing used in the standard care arm (non-antimicrobial and antimicrobial)

5. SUBJECTS

5.1 Anticipated number of research subjects

Below a summary is given for the sample size needed. The primary outcome, wound status (healed vs non-healed) is used for sample size calculation for both randomisation groups.

The sample size calculation has been performed using GPower freeware sample size calculator, based on 2x2 Chi-squared test for wound healed status. Power calculation for sample size assumes 80% power and 5% two-sided confidence interval.

Table 4: standard care vs MedCu dressing. The hypothesis is that MedCu dressing performs better to a minimum 20% (effect size 0.41) in wound healed at week 12.

Since some patients may withdraw over the course of the 12-week trial period, a 20% dropout rate is calculated into each sample size. A 1:1 allocation to the two types of dressing is applied.

Note: There will be an option to expand sample size, subject to no safety concerns after initial sample size has been reached. This then allows wound healing comparison for purer sample of 'leg ulcers' and 'foot ulcers' separately from each other. For this purpose, the same effect size will be applied. The hypothesis is that MedCu dressing performs better to a minimum 20% (effect size 0.40), requiring a sample size 66 (taking into account same 30% drop-out/withdrawal rate)

Table 4, Sample size calculations

Sample size calculation		
	Standard care control dressing	Intervention dressing (MedCu copper dressing)
Ulcer healed	40%	60%
Ulcer not healed	60%	40%
	Power beta of 80%, Alpha p-value of 0.05, effect size 0.40 Sample size required without any drop-out: 50 patients Sample size with 30% attrition rate included: 66 patients Total of 66 patients, distributed as: - 33 Patients to receive MedCu dressing - 33 Patients to receive standard care dressing	

The CONSORT guidelines require a statement on the number of patients assessed for eligibility (Schulz, Altman & Moher 2010). The number of patients screened but who did not meet the inclusion criteria or who declined to participate will be recorded, as will any patients who are lost to follow-up (Appendix 5).

5.1.1 Randomisation and Blinding aspects

Following written consent patients will be allocated at random to the one of two treatment arms. Participants are stratified by ulcer size (PUSH score) at baseline , ie week 0.

A non-restricted randomised sequence will generated for each of the two groups using a freeware randomisation programme, see https://www.sealedenvelope.com/. The randomisation will be stratified by ulcer size, with one group being those with a PUSH score of up to and including 8, or a PUSH score of 9 or higher

Each next randomisation allocation will be obtained from the sealedenvelope.com account for this CUPRA trial.

As the study involves different looking dressings, it is not possible to achieve blinding for the participants. However, statistical analysis is carried out blinded to group allocation, by persons who have not had contact with study participants.

5.2 Eligibility criteria

5.2.1 Inclusion criteria

- Aged 18 years or over
- Women to be of non-childbearing potential (ie post-menopausal)
- Lower limb ulcer sized between 1 to 30 cm^2
- Patients can be newly presenting to or existing users of the specialist service in question
- Patients with recurrent wounds, including multiple wounds, are eligible; largest eligible (ie <30cm^2) ulcer to be index wound
- If infection occurs and systemic antibiotics applied, whilst in study, then this is not deemed an exclusion criterion.
- Chronicity: clinical diagnosis of ulcer with wound duration > 30 days and < 1 year from patient becoming aware.
- Prophylactic systemic antibiotic use is not an exclusion criterion
- Mental and physical ability to give consent and complete study activities
- Underlying pathology of lower limb ulcer can be venous, mixed venous-arteria, arterial, or through different underlying aetiology. Recognised co-morbidities that may contribute to the development of lower limb ulcers (e.g. diabetes, rheumatoid arthritis, peripheral vascular disease) are not an exclusion criterion.
- For leg ulcers: Patient is suitable for, and willing to wear, compression therapy, or valid clinical reason why they should not be prescribed compression therapy.

5.2.2 Exclusion criteria

- Under the age of 18 years
- Unable to fully understand the consent process and provide informed consent due to either language barriers or mental capacity

- Limited life expectancy, i.e. undergoing palliative care, or other condition that in opinion of researcher contraindicates participation
- Active infection in lower limb ulcer treated with systemic antibiotics within last 1 week (does not apply for prophylactic antibiotic regimes)
- Enrolled in other interventional research study related to patient's lower limb ulcer
- Previous participation in CUPRA study
- Awaiting significant surgical intervention related to vascular or skeletal system of the lower limbs, planned within three months (ie 12 week trial period)
- Known intolerance or allergy to materials used in MedCu copper dressing.

5.3 Early withdrawal of subjects

Patients have the right to withdraw from the trial at any time and without giving any reason. If a patient withdraws from the trial, any and all information gathered prior to the withdrawal will be included in the analysis, though no further data collection will occur. If a patient does not attend planned follow-up appointments then two more attempts will be made to contact the patient regarding the study. If still no contact can be made then the patient is deemed lost to follow-up and any collected study data will be retained. Appendix 2, INTERVENTION DEVIATION AND LEG ULCER INFECTION, covers study withdrawals in more detail.

6. SAFETY

6.1 Potential risks & benefits to study participants

There is no anticipated personal safety risk associated with taking part in this study. If the research team learns of important new information that might affect patient's desire to remain in the study, he or she will be told. Appropriate precautions are in place to ensure medical and personal information is kept safe through adhering to appropriate governance regulations. Participants in both the treatment arms will be allocated a wound dressing that is used for its intended licensed purpose and that is available via standard care routes. Any adverse events will be recorded, as outlined in sections below.

Apart from being allocated to a different type of wound dressing, all patients will receive the indicated clinical care they would receive when not in the trial. They will otherwise be cared for in exactly the same manner as they normally would. Participants cannot claim payments, reimbursement of expenses or any other benefits or incentives for taking part in this research.

6.2 Safety definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or other clinical investigation participant taking part in a trial of a medical device, which does not necessarily have to have a causal relationship with the device under investigation.

	An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the device, whether or not considered related to the device.
Serious Adverse Event	A serious adverse event is any untoward medical occurrence that: - results in death - is life-threatening - requires inpatient hospitalisation or prolongation of existing hospitalisation - results in persistent or significant disability/incapacity - consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

6.3 Procedures for recording adverse events

All SAEs need to be reported to the sponsor/host Trust R&D **within one working day** of the investigator team becoming aware of them.

The relationship of each adverse event to the trial must be determined by a medically qualified individual according to the following definitions:

- **Related**: The adverse event follows a reasonable temporal sequence from intervention. It cannot reasonably be attributed to any other cause.
- **Not Related**: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

7. STATISTICAL CONSIDERATION AND DATA ANALYSIS PLAN

7.1 Analysis of baseline characteristics

To determine the demographics and characteristics of the patients, the following baseline data will be collated:

Patient details

- Age
- Sex
- Height, Weight, BMI

- Smoking status
- Postcode (deprivation score)
- Mobility status: does not walk / walks with assistance (stick/frame) / walks without assistance.

Medical history and status:

- Significant comorbidities, including CEAP Clinical score, Peripheral Arterial Disease, Diabetes (type I, type II, +/- neuropathy), Heart failure, Eczema, Psoriasis, Other dermatitis, Cancer
- Any previous lower limb ulcers (within last 2 years).

Index lower limb and ulcer status

- ABPI (within last 3 months) , or reason for non-measurement
- Ulcer location: above malleolar region (ie leg) / spanning malleolar region (ie ankle) / below malleolar region (ie foot)
- Chronicity of ulcer (in weeks)
- Ulcer size (PUSH score / digital Healthy io App)
- If lower limb ulcer healed at week 4 and/or week 8, status of index location at week 12 (ie any recurrence of ulcer?)

Dressing care characteristics

- Frequency of care (change of dressing: …. per week.
- 'Prescribed' compression bandaging: yes / no
- Which specific dressing used on wound ?

Any differences in distribution will be established with Chi-squared test or ANOVA as indicated.

7.2 Primary outcome statistics

The primary objective for this pilot study wound healed status at week 12.

For comparative performance (superiority) analysis, any statistically significant difference (p-value < 0.05) between the two treatment arms will be determined with Chi-squared test.

Analyses will be performed on a per protocol basis, with only those participants that data is available for included in the analysis. Data will first be collated in Microsoft Excel, followed by analyses performed using SPSS v20.

7.3 Secondary outcome statistics

To evaluate the effect of the different dressing regimes on lower limb ulcer healing, data from the two treatment arms will be compared.

Ulcer healing and more general health measures is assessed by the following parameters:

- Ulcer status (healed vs non-healed)

- Ulcer size (cm^2, measured with wound measuring App)
- PUSH score
- VEINES-Sym (scores for individual questions, 9 questions)
- EQ-5D-5L

To assess the Ulcer size, which are measured every 4 weeks, per treatment arm the average difference between time points will be calculated per treatment group (Wilcoxon test). To compare between the groups, Mann-Whitney U-test will be applied.

To measure patient-reported outcome measures on VEINES-Sym at baseline, week4 , week 8 and week 12 (and EQ-5D-5L for week 0 and week 12); the Wilcoxon test will be applied within treatment arms (over time) whereas the Mann-Whitney U-test will be performed between treatment arms. Data of the two treatment arms will be compared by applying the Mann-Whitney U-test.

Subject to sufficient data being available, Cox proportional hazards regression analysis will be conducted to investigate the role of the dressing itself and other covariates in ulcer healing rates. Other covariates include: ulcer size and chronicity at baseline, patient age, ulcer aetiology, absence/presence of co-morbidities, ulcer location, history of recurrent ulcers.

The following descriptive statistics will be reported on where possible:

- Number of patients screened
- Number of patients eligible/ineligible, and percentage of patients consented into the trial
- Number of patients completed the trial/discontinued (plus reasons if discontinued)

8. DATA HANDLING AND MONITORING

Data arising from this study is confidential. Identifiable information can only be accessed by delegated members of the study team. Anyone in the research team who does not have a substantive contract with North Cumbria Integrated Care NHS Foundation Trust will need to apply for a letter of access via the NIHR research passport scheme, should they require access to identifiable study data.

Patient identifiable data will only be used within each respective Trust and by the core research team. All identifiable data is stored on password protected NHS computer systems. Anonymised data will be shared and stored using security-enabled systems such as password-protection and encryption of e-mails and files. The requirements of the Data Protection Act, GDPR, and NHS Code of Confidentiality will be followed at all times. All researchers will be fully trained in NHS Confidentiality and GCP. Participants' GP practices will be informed that they are taking part in the study.

All paper data will be held in secure locked environments in the office of the Research & Development department in the Carlisle, Whitehaven, Workington and Wigton hospital locations. Data released (e.g. by publication) will contain no information that could lead to the identification of an individual participant. Upon completion of the study the site files will be archived for a period of 10 years in line with local archiving policy and procedures. Direct access to data only will be granted to authorised representatives from the sponsor / host institution, grant funder and medical device

provider Creed Health, and the regulatory authorities to permit trial-related monitoring, audits and inspections.

This investigator-initiated trial will be monitored in terms of conduct of the study by the in-house research team, led by the Chief Investigator, who will convene on a monthly basis in person or via phone/e-mail. A trial steering committee will not be convened for this trial. The study can be audited by the in-house R&D department as part of their rolling audit programme of sponsored and hosted research studies. As part of the research grant agreement, anonymised study data will be shared with both MedCu company for review and for potential publication purposes. No identifiable data, including on potential exemplar case photos, will be contained in any of this data.

9. GOVERANCE OF STUDY

9.1 Approvals

This study will be conducted in compliance with the protocol approved by the Health Research Authority, National Research Ethics Service, and local Trust R&D Approval, and according to Good Clinical Practice standards including the Declaration of Helsinki (1964, Amended Oct 2013). No deviation from the protocol will be implemented without the prior review and approval of the aforementioned review bodies, except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported according to policies and procedures

9.2 Sponsor & Indemnity

North Cumbria Integrated Care NHS Foundation Trust is the sponsor of this study and therefore NHS indemnity applies for design, conduct and management of the study. MedCu company has provided a grant for this study by means of provision of the dressing, worth £3,500.

Patients will not be given financial incentives for taking part in the study. Travel expenses are not offered in this study since patients are seen in clinic as part of their normal care pathway.

9.3 Medical Device management and use of different compression bandage brands

MedCu dressings will be stored in the NHS store and clinic rooms at the temperature recommended by the respective manufacturers. No requirement for involvement pharmacy or clinical trials pharmacist. Standard approved and available stocks of dressings and compression bandaging to be used for any standard care activities.

9.4 End of Study

This will be the date of the final research visit of the last participant across the whole trial.

10. PUBLICATION AND DATA-SHARING POLICY

The study will be registered on the ISRCTN website, in line with CONSORT guidelines on good practice in clinical research.

The results of this study will be disseminated through:

- Peer-reviewed manuscript in scientific journal
- Internal report

11. REFERENCES

Agale SV. Chronic leg ulcers: epidemiology, aetiopathogenesis, and management. Ulcers. 2013 Apr 22;2013.

Bergan JJ, Schmid-Schönbein GW, Smith PD, Nicolaides AN, Boisseau MR, Eklof B. Chronic venous disease. New England Journal of Medicine. 2006 Aug 3;355(5):488-98.

Borkow G, Gabbay J. Copper as a biocidal tool. Curr Med Chem 2005;12(18): 2163-75. DOI: 10.2174/0929867054637617

Borkow G, Roth T, Kalinkovich A. Wide spectrum potent antimicrobial efficacy of wound dressings impregnated with cuprous oxide microparticles. Microbiology Research 2022;13(3): 366-76. DOI: 10.3390/microbiolres13030029

Burian EA, Sabah L, Karlsmark T, Kirketerp-Møller K, Moffatt CJ, Thyssen JP, Ågren MS. Cytokines and venous leg ulcer healing—a systematic review. International Journal of Molecular Sciences. 2022 Jun 10;23(12):6526.

Eberhardt, R.T,& Rafetto, J.D. (2005) 'Chronic venous insufficiency', *Circulation,* 111(18) pp.2398-2409.

Eklof B, Rutherford RB, Bergan JJ, Carpentier PH, Glovicski P, Kistner RL, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Sur 2004;40:1248-52

Franks PJ, Barker J, Collier M, Gethin G, Haesler E, Jawien A, Laeuchli S, Mosti G, Probst S, Weller C. Management of patients with venous leg ulcers: challenges and current best practice. Journal of wound care. 2016 Jun 1;25(Sup6):S1-67.

Gardner SE, Haleem A, Jao YL, Hillis SL, Femino JE, Phisitkul P, Heilmann KP, Lehman SM, Franciscus CL. Cultures of diabetic foot ulcers without clinical signs of infection do not predict outcomes. Diabetes Care. 2014 Oct 1;37(10):2693-701.

Gerard C, Bordeleau LJ, Barralet J, Doillon CJ. The stimulation of angiogenesis and collagen deposition by copper. Biomaterials 2010;31(5): 824-31. DOI: 10.1016/j.biomaterials.2009.10.009

Gonzalez-Consuegra, R.V. & Verdu, J. (2011) 'Quality of life in people with venous leg ulcers', *Journal of Advanced Nursing,* 67 (5), pp. 926-944.

Gorel O, Hamuda M, Feldman I, Kucyn-Gabovich I. Enhanced healing of wounds that responded poorly to silver dressing by copper wound dressings: Prospective single arm treatment study. Health Science Reports. 2024 Jan;7(1):e1816.

Graham, I.D., Harrison, M.B., Nelson, E.A., Lorimer, K. & Fisher, A. (2003) 'Prevalence of lower limb ulceration: a systematic review of prevalence studies', *Advanced Skin Wound Care,* 16(6) pp.305-316.

Graves N, Phillips CJ, Harding K. A narrative review of the epidemiology and economics of chronic wounds. British Journal of Dermatology. 2022;187(2):141-8.

Grothier, L., & Stephenson, J. (2015). An audit to determine the clinical effectiveness of a pathway for managing wound infection. Wounds UK, 11(2), 32-40.

Guest JF, Fuller GW, Vowden P. Cohort study evaluating the burden of wounds to the UK's National Health Service in 2017/2018: update from 2012/2013. BMJ open. 2020;10(12):e045253.

Halbert, A.R., Stacey, M.C., Rohr, J.B. and Jopp-Mckay, A., 1992. The effect of bacterial colonization on venous ulcer healing. Australasian journal of dermatology, 33(2), pp.75-80.

Harding K, Gottrup F, Jawień A, Mikosiński J, Twardowska-Saucha K, Kaczmarek S, Sopata M, Shearman C, Pieronne A, Kommala D. A prospective, multi-centre, randomised, open label, parallel, comparative study to evaluate effects of AQUACEL® Ag and Urgotul® Silver dressing on healing of chronic venous leg ulcers. International Wound Journal. 2012 Jun;9(3):285-94.

Hareendran, A., Bradbury, A., Budd, J., Geroulakos, G., Hobbs, R., Kenkre, J., & Symonds, T. (2005). Measuring the impact of venous leg ulcers on quality of life. *Journal of Wound Care*, *14*(2), 53-57.

Hon J, Lagden K, McLaren AM, O'Sullivan D, Orr L, Houghton PE, Woodbury MG. A prospective, multicenter study to validate use of the PUSH in patients with diabetic, venous, and pressure ulcers. Ostomy/wound management. 2010 Feb;56(2):26-36.

Hulley SB, Cummings SR, Browner WS, Grady D, Newman TB. Designing clinical research : an epidemiologic approach. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013. Appendix 6C, page 79 (via https://sample-size.net/correlation-sample-size/ , last accessed 4 June 2024.

Kim ES, Sharma AM, Scissons R, Dawson D, Eberhardt RT, Gerhard-Herman M, Hughes JP, Knight S, Marie Kupinski A, Mahe G, Neumyer M. Interpretation of peripheral arterial and venous Doppler waveforms: A consensus statement from the Society for Vascular Medicine and Society for Vascular Ultrasound. Vascular Medicine. 2020 Oct;25(5):484-506.

Kolahreez D, Ghasemi-Mobarakeh L, Liebner F, Alihosseini F, Quartinello F, Guebitz GM, Ribitsch D. Approaches to Control and Monitor Protease Levels in Chronic Wounds. Advanced Therapeutics. 2024 May;7(5):2300396.

Kornblatt AP, Nicoletti VG, Travaglia A. The neglected role of copper ions in wound healing. J Inorg Biochem 2016;161: 1-8. DOI: 10.1016/j.jinorgbio.2016.02.012

Kumar A, Pandit V, Nagaich U. Therapeutic evaluation of chemically synthesized copper nanoparticles to promote full-thickness excisional wound healing. Int J Applied Pharmaceutics 2020;12(6): 136-42.

Lamping DL, Schroter S, Kurz X, Kahn SR, Abenhaim L. Evaluation of outcomes in chronic venous disorders of the leg: development of a scientifically rigorous, patient-reported measure of symptoms and quality of life. Journal of vascular surgery. 2003 Feb 1;37(2):410-9.

Launois R. Health-related quality-of-life scales specific for chronic venous disorders of the lower limbs. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2015 Apr 1;3(2):219-27.

Lavery LA, Armstrong DG, Wunderlich RP, Mohler MJ, Wendel CS, Lipsky BA. Risk factors for foot infections in individuals with diabetes. Diabetes care. 2006 Jun 1;29(6):1288-93.

Lin EP, Bhatt S, Rubens D, Dogra VS. The importance of monophasic Doppler waveforms in the common femoral vein: a retrospective study. Journal of ultrasound in medicine. 2007 Jul;26(7):885-91.

Lu W, Rao A, Oropallo A, Gawlik S, Haight J. Use of Copper Nanoparticles to Reduce Bioburden in the Treatment of Diabetic Foot Ulcers. Eplasty. 2022;22.

Melamed E, Borkow G. Continuum of care in hard-to-heal wounds by copper dressings: a case series. Journal of Wound Care. 2023 Dec 2;32(12):788-96.

Melamed E, Rovitsky A, Roth T, Assa L, Borkow G. Stimulation of healing of non-infected stagnated diabetic wounds by copper oxide-impregnated wound dressings. Medicina. 2021 Oct 19;57(10):1129.

Ndosi M, Wright-Hughes A, Brown S, Backhouse M, Lipsky BA, Bhogal M, Reynolds C, Vowden P, Jude EB, Nixon J, Nelson EA. Prognosis of the infected diabetic foot ulcer: a 12-month prospective observational study. Diabetic Medicine. 2018 Jan;35(1):78-88

NICE (National Institute for Health and Care Excellence), Clinical Guideline for venous leg ulcers, https://cks.nice.org.uk/topics/leg-ulcer-venous/, last accessed 24 May 2024

NICE (National Institute for Health and Care Excellence), NICE Guideline 19, Diabetic foot problems: prevention and management, https://www.nice.org.uk/guidance/ng19 , last accessed 24 May 2024

O'Brien ME, Murray G, Gogoi D, Yusuf A, McCarthy C, Wormald MR, Casey M, Gabillard-Lefort C, McElvaney NG, Reeves EP. A review of alpha-1 antitrypsin binding partners for immune regulation and potential therapeutic application. International Journal of Molecular Sciences. 2022 Feb 23;23(5):2441

Oczkowski SJ. A clinician's guide to the assessment and interpretation of noninferiority trials for novel therapies. Open Medicine. 2014;8(2):e67.

Pillen, H., Miller, M., Thomas, J., Puckridge, P., Sandison, S. & Spark, J.I. (2009) 'Assessment of wound healing: validity, reliability and sensitivity of available instruments', *Wound Practice and Research,* 17(4) pp. 208-217.

Porter JM, Moneta GL. Reporting standards in venous disease: an update. International Consensus Committee on Chronic Venous Disease. J Vasc Surg 1995;21:635-45

Raffetto JD, Ligi D, Maniscalco R, Khalil RA, Mannello F. Why venous leg ulcers have difficulty healing: overview on pathophysiology, clinical consequences, and treatment. Journal of clinical medicine. 2020 Dec 24;10(1):29.

Ratliff, C.R. & Rodeheaver. G.T. (2005) 'Use of the PUSH tool to measure venous ulcer healing', *Ostomy Wound Management,* 51(5) p.58.

Salah I, Parkin IP, Allan E. Copper as an antimicrobial agent: Recent advances. RSC advances. 2021;11(30):18179-86.

Sen CK, Khanna S, Venojarvi M et al. Copper-induced vascular endothelial growth factor expression and wound healing. Am J Physiol Heart Circ Physiol 2002;282(5): H1821-H7. DOI: 10.1152/ajpheart.01015.2001

Serena TE, Bayliff SW, Brosnan PJ, DiMarco DT, Doner BA, Guthrie DA, Patel KD, Sabo MJ, Samies JH, Carter MJ. Bacterial protease activity as a biomarker to assess the risk of non-healing in chronic wounds: Results from a multicentre prospective cohort clinical trial. Wound Repair and Regeneration. 2021 Sep;29(5):752-8.

SIGN (2010) Management of Chronic Venous Leg Ulcers. Edinburgh: SIGN.

Smith, J.J., Guest, M.G., Greenhalgh, R.M., Davies, A.H. (2010) 'Measuring the quality of life in patients with venous ulcers', *Journal of Vascular Surgery,* 31 pp.642-649.

Stacey MC. Biomarker directed chronic wound therapy–a new treatment paradigm. Journal of Tissue Viability. 2020 Aug 1;29(3):180-3.

Stotts, N. A., Rodeheaver, G. T., Thomas, D. R., Frantz, R. A., Bartolucci, A. A., Sussman, C., ... & Maklebust, J. (2001). An instrument to measure healing in pressure ulcers development and validation of the Pressure Ulcer Scale for Healing (PUSH). *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *56*(12), M795-M799.

Thomson PD, Smith Jr DJ. What is infection?. The American journal of surgery. 1994 Jan 1;167(1):S7-11.

Tuttle MS. Association between microbial bioburden and healing outcomes in venous leg ulcers: a review of the evidence. Advances in wound care. 2015 Jan 1;4(1):1-1.

APPENDIX 1. INTERVENTION DEVIATION AND LOWER LIMB ULCER INFECTION

There may be incidences where a participant may either:

- Develop a reaction to the allocated dressing.
- Becomes completely non-compliant (possibly due to allocated dressing being uncomfortable, or eg hospital admission)
- Improve to such an extent that allocated dressing is no longer indicated.

In such instances the patient and/or clinician can opt to stop or pause treatment with the dressing in question. If this occurs, this needs to be recorded (date and reason), and the decision can then be made to either:

- Discontinuation of intended dressing due to improvement in symptoms (including wound healed). Participant will still continue to be assessed as per planned dates and timepoints.
- Change over to an alternative dressing that is not the originally allocated type. This is allowed but only if there are clinical indications to do so or at patient request if they cannot tolerate the allocated dressing. Patient can later in trial period be transferred back to original allocated bandage type if required.
- Pausing or discontinuation of wound dressing when not clinically indicated. Even if lower limb ulcer persists and patient no longer wears allocated dressing, they can still continue in the trial if they wish. Outcome measures will continue to be recorded as per planned dates and time points.
- Pause or discontinuation due to adverse event. Patient can remain in trial provided they are capable to continue with follow-up schedule and completion of outcome measures. If not possible, see next point regarding 'Withdraw patient from study'.
- Withdraw patient from study.
    - At the request of the patient
    - For clinical reasons, eg if the leg ulcer has deteriorated to such an extent that emergency surgical or medical intervention is required which means return to use of any dressing in reasonable time frame (within time to next trial follow-up visit) is not feasible. In this case, this needs to be reported as a (Serious) Adverse Event if discontinuation is due to deterioration of the index wound or index leg only.

When overall trial participation for a patient is finished early, the participant will still be asked to complete the relevant questionnaires (provided they have capacity to do so):

- Week 4, week 8 and week 12 VEINES Sym questionnaire
- Week 12 EQ5D5L QoL questionnaire

Infection and use of antibiotics during trial

Patients do not have to withdraw from the study if clinically determined infection occurs, as long as clinically there is a reason to continue with wound dressing and it is deemed safe to do so. This applies for both oral and intravenous antibiotics use. If a treating clinician determines that the allocated dressing should stop then this will be classed as an intervention deviation – see above.

APPENDIX 2 – CUMBRIA WOUND FORMULARY (2024)

Please see https://medicines.necsu.nhs.uk/cumbria-wound-formulary/

APPENDIX 3. STUDY PARTICIPANT FLOWCHART