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Wool-derived keratin dressings versus usual care dressings for treatment of slow-healing venous leg ulceration: study protocol for a randomised controlled trial (Keratin4VLU)

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ABSTRACT

Introduction Keratins, filament-forming proteins found in vertebrate epithelium, are downregulated in slow-healing venous leg ulcers (VLU) compared with normal-healing VLU. Laboratory and animal model research has suggested exogenous keratins increase expression of endogenous keratins. A non-randomised controlled trial of an exogenous keratin dressing reported increased healing in slow-healing VLU. To date, no randomised controlled trial has been done to verify these promising findings.

Methods and analysis The Keratin4VLU trial is a single-blind, pragmatic, parallel group, randomised controlled trial of keratin dressings compared with usual care non-medicated dressings in patients with VLU where either (1) the ulcer area is greater than 5 cm^2, (2) the ulcer has been present for more than 26 weeks or (3) both. All patients will receive compression therapy. The primary outcome is the proportion of patients with healed VLU at 24 weeks after randomisation as adjudicated by blinded review of an ulcer photograph. Secondary outcomes are time to healing, estimated change in ulcer area, change in health-related quality of life, agreement between blinded and unblinded assessors and adverse events. The analysis will be intention-to-treat on the primary and secondary outcomes (excepting health-related quality of life).

Ethics and dissemination The Keratin4VLU trial received ethical approval from the Northern A Health and Disability Ethics Committee. We plan to publish the results within 1 year of trial completion and will include the results on the trial registration page.

Trial registration number NCT02896725; Pre-results.

Strengths and limitations of this study

- This trial is a pragmatic trial using five experienced study centres and was designed to maximise external validity.
- This trial uses a validated prognostic index to stratify randomisation by probability of healing within 6 months, ensuring prognostic balance between groups within the study centres.
- The main limitation in the trial design is the single-blind outcome assessment for healing outcomes—being open label for all other outcomes, for example, health-related quality of life and incidence of adverse events may introduce bias into those outcome assessments.

INTRODUCTION

Venous leg ulcers (VLU) can be categorised into 'normal-healing' and 'slow-healing' groups by a prognostic index on the basis of two factors that are associated with non-healing after 24 weeks of treatment with compression: (1) VLU area greater than 5 cm^2 at baseline and/or (2) VLU present for more than 6 months at baseline.[1] In trials with broad inclusion criteria, including our own trials, 50%–70% of participants have either one or both of these factors and are thus likely to be slow healing.[2–4] Trials that recruit only those participants with prognostically slow-healing VLU report delayed time to healing (eg, median time to healing 245 days)[5 6] compared with trials that recruit participants with any type of VLU (eg, median time to healing 92–98 days).[2 3]

There is trial evidence for the effectiveness of a category of dressing referred to as 'skin substitutes' derived either from live cellular or acellular products in slow-healing ulcers.[7] However, evidence from trials of one type of skin substitute dressing cannot be extrapolated to the other types of skin substitute dressings. A dressing manufactured from keratins derived from New Zealand sheep wool, freeze-dried with glycerol into a matrix that delivers the keratins onto the wound bed as the matrix dissolves is an acellular skin substitute dressing.

Keratins are filament-forming proteins found in vertebrate epithelium and are produced by activated keratinocytes. In acute wounds keratinocytes migrate from the

wound margins, proliferating and releasing cytokines to initiate tissue response. However, in chronic wounds, such as ulcers, keratinocytes appear to be unable to migrate, leaving this phase of wound healing incomplete.[8] Keratins 6, 16 and 17 are required for such migration,[9] but in punch biopsies from slow-healing VLU, these keratins have been found to be downregulated when compared with punch biopsies from healing VLU.[10] Introducing exogenous wool-derived keratins promotes in vitro keratinocyte migration.[11] This finding is supported by in vivo porcine research that found wounds healed earlier with a wool-derived keratin dressing than with a standard dressing or no dressing.[12] Quantitative PCR analysis of wound biopsies from the same experiment showed endogenous keratin was expressed earlier in wounds treated with wool-derived keratin, suggesting the exogenous keratin was inducing keratinocyte migration and endogenous keratin expression, not simply donating exogenous keratin to the healing process.

Human model evidence for treating VLU with keratin dressings has been limited to case reports, a case series study and a small non-randomised controlled trial. In the case series of 23 patients with VLU in Christchurch, New Zealand, involving 255 dressing changes over 12 weeks, investigators examined the acceptability of wool-derived keratin dressing materials used under compression.[13] Most patients (97%) reported a willingness to use the dressing again and 82% found it preferable to their previous dressings. In the non-randomised trial, set in a University Clinic in China, 55 patients with slow-healing VLU (area >5 cm^2 that did not respond to 3 months standard treatment) were assigned to receive treatment with keratin dressings (n=31) or a traditional herbal preparation (n=24) for up to 24 weeks.[14] All participants received a standard compression therapy (four-layer compression bandaging) over the keratin dressing. Complete VLU healing was significantly more frequent in the keratin dressing group compared with the standard care group (61.3% vs 25.0%, risk difference 36.3%, 95% CI 11.9% to 60.7%). Adverse event rates (infection, pruritus and pain) were lower in the keratin dressing group.

While the evidence base for keratin dressings is suggestive, a well-designed definitive randomised controlled trial is required to identify the actual treatment effect in a population similar to people typically seen in clinical practice.

METHODS AND ANALYSIS

Trial design

Keratin4VLU will be a prospective pragmatic, community-based, single-blind, parallel group, randomised controlled trial with participants receiving either a keratin dressing or usual care dressing until healing (or censoring at trial end, whichever is sooner). Block randomisation will be used, stratified by study centre and prognostic index (ulcer size and duration) to ensure a balance of participants within study centres to isolate any centre effect. Participants in both arms will receive compression therapy (specific compression system guided by patient and/or clinical preference), which is standard care delivered by district nursing services at the study centres. The district nurse will identify potential participants, obtain verbal consent from them to be contacted by the research nurse if the patient is interested in the trial and notify the research nurse at each trial centre.

The aim of this trial is to evaluate the effectiveness of a keratin dressing when used in addition to compression therapy on patients with slow-healing VLU by assessing the proportion of patients at 24 weeks with healed VLU.

Recruitment

Patients with VLU who present for treatment or are already receiving treatment from the community-based district nursing services at study centres previously involved in the National Institute for Health Innovation's leg ulcer trials will be recruited. These centres are based in New Zealand at the Auckland, Counties Manukau, Waikato and Southern District Health Boards, and Nurse Maude community nursing services in Christchurch. A 0.5 full-time equivalent research nurse has been seconded to the trial from each study centre (for which the employing authority is to be reimbursed).

Potentially eligible patients will be identified by and notified to research nurses by district nurses (figure 1). The research nurses will screen these patients for eligibility and obtain informed consent to participate. Eligible patients will be treated for 2 weeks with compression therapy to ensure compliance with compression, reassessed for eligibility and randomised by the research nurse at a location convenient to the patient (a clinic, the patient's home or workplace) at week 0. If randomised to the keratin dressing group, the keratin dressings will be left with the patient; if allocated to usual care, dressing selection will be guided by the district nurses' clinical judgement and patient preference. The research nurse will also conduct up to two endpoint visits: one endpoint visit will occur at 24 weeks after randomisation for all participants. The second endpoint visit will only occur if the participant's VLU is reported as healing during the trial, either before or after the 24-week visit.

The five study centres all recruited participants for the Aspirin4VLU trial.[15] To December 2016, they had screened an average of 78 patients with VLU in compression per month. Assuming the same number presents each month in the Keratin4VLU trial, 1404 patients with VLU would present to the study centres over the 18-month recruitment period.

The Honey as Adjuvant Leg ulcer Therapy (HALT) trial found that 54% of those randomised had a prognostic score indicating they were 'slow healers',[4] while the baseline data from the Aspirin4VLU trial indicated 45% were 'slow healers'.[15] On this basis, we assume about half of 1404 patients will be eligible because they are 'slow healers', and therefore a pool of about 700

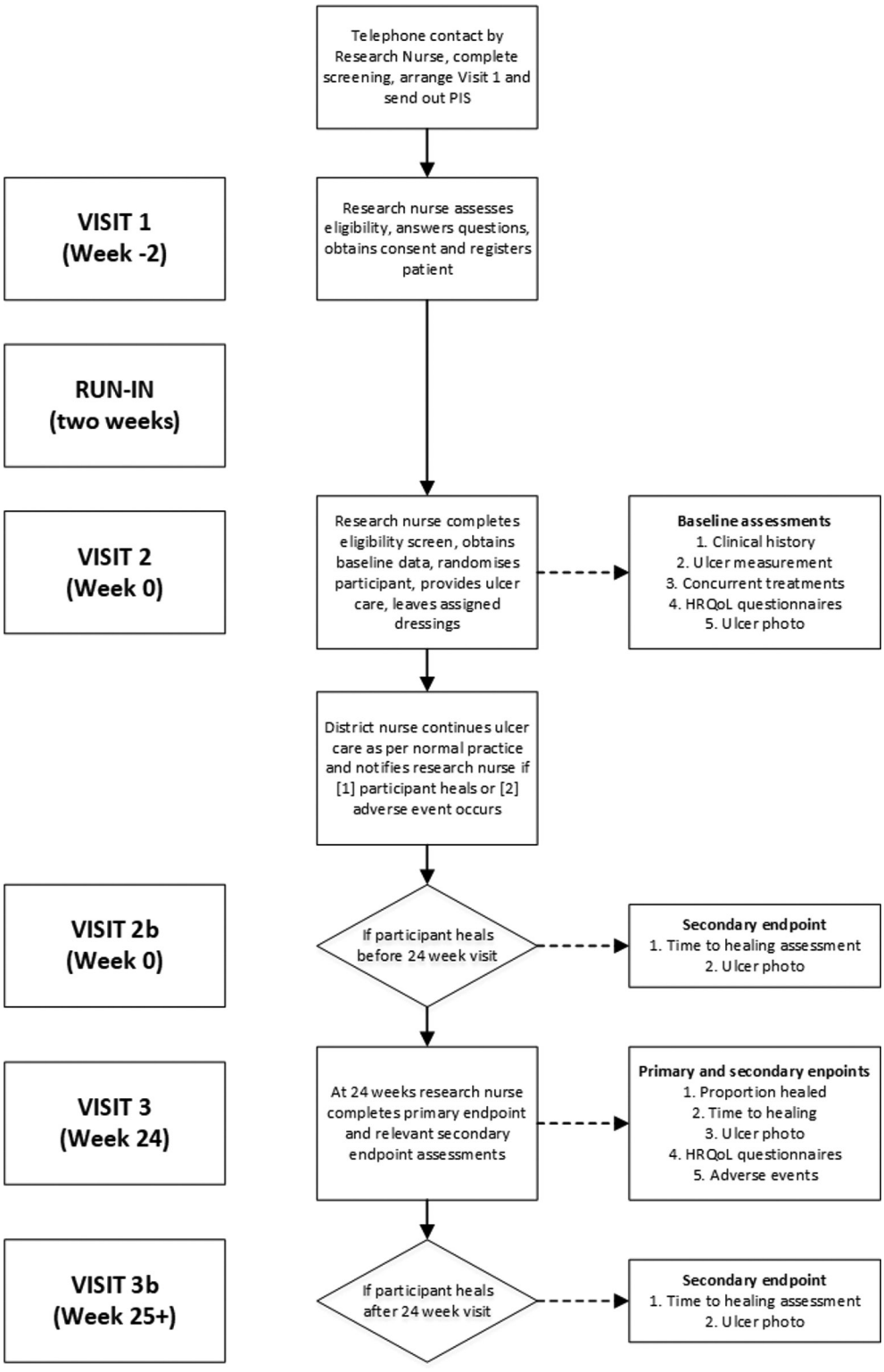

Figure 1 Detailed trial schematic showing participant contacts and measures. HRQoL, health-related quality of life; PIS, participant information sheet.

patients with VLU would be eligible to take part in the proposed trial. We are confident of high participation rates, based on our past experience showing patients with VLU are motivated to participate in research: the conversion rate of registered patients meeting the inclusion criteria to randomised participants in two previous trials was 93% and 100%,[4 16] while the conversion rate in the Aspirin4VLU trial was 83% of those registered.[15] Assuming only 45% of eligible participants accept an invitation to participate, with our relatively open criteria, we estimate 18 months will be a sufficient recruitment period.

Case definition

For the purposes of this trial, an incident ulcer will be considered to be any break in the skin on the leg (below the knee) that has been present for 4 or more weeks. If a patient known to a service presents with a new episode of ulceration, has a history of VLU, is considered to have a current VLU, they will be candidates for participation. Patients already in treatment with prevalent ulcers meeting the case definition will also be eligible for inclusion. A patient will be considered to have a purely VLU where other causative aetiologies (peripheral vascular disease, diabetes, rheumatoid arthritis, malignancy) have been ruled out, the ulcer appears clinically venous (presentation may include any or all of the following: moist, shallow, irregular shape; haemosiderin pigmentation; venous eczema; ankle oedema; ankle flare; lipodermatosclerosis) and an Ankle Brachial Index ≥0.7 to rule out significant arterial insufficiency.

Only patients with slow-to-heal VLU being treated through the trial centres will be recruited. Patients will be categorised as slow-to-heal at baseline where they have either (1) a VLU with an area that is greater than 5 cm^2 or a VLU that has been present for greater than 6 months or (2) a VLU that meets both the previous conditions in (1). The absence of these criteria is associated with increased likelihood of healing at 24 weeks when receiving compression therapy (normal healing) while the presence of these criteria is associated with decreased likelihood of healing at 24 weeks when receiving compression therapy (slow healing).[1]

Inclusion criteria

Patients with leg ulcers will be eligible for inclusion if they are aged 18 years or older and able to provide written informed consent, determined to have a VLU, able to tolerate compression therapy (during the 2-week run-in phase) and have a slow-healing VLU.

Exclusion criteria

Potentially eligible participants will be excluded if they have a hypersensitivity to wool or wool alcohol (lanolin), a VLU with exposed bone or tendon, an infected VLU requiring treatment with antibiotics, a localised infection requiring a medicated dressing (silver-impregnated , iodine-impregnated or honey-impregnated, or polyhexamethylene biguanide dressing), a history of rheumatoid arthritis or vasculitis, uncontrolled diabetes (defined as glycosylated haemoglobin >100 mmol/mol), severe liver failure (indicated by jaundice), severe heart failure (defined as short of breath while seated) or renal failure defined as estimated glomerular filtration rate <30), severe peripheral arterial disease (defined by inability to walk even short distances without pain), suspected or diagnosed skin malignancy associated with leg ulcer, any other threat to safe participation or do not complete the 2-week run-in phase. Patients with infection requiring treatment with antibiotics or a medicated dressing at registration may be eligible for participation once the infection resolves.

Consent

All participants will receive a six-page participant information sheet (PIS) that incorporates the informed consent form. The PIS outlines in simple terms the trial design, the interventions, safety issues, and risks and benefits along with an invitation to participate if interested (available from the corresponding author on request). The research nurses will discuss the PIS with potential participants as well as any other persons the participant wishes to include. Participants must give written informed consent if they wish to participate. Participation is voluntary and participants will be free to withdraw at any time without influencing their usual treatment. Only the participants are able to consent and two copies will be each signed by the participant and the research nurse; one copy will be retained by the participant and one copy will be kept in the participant trial folder for monitoring purposes. Informed consent will be obtained before the participant can be entered into the run-in phase of the trial.

Randomisation and allocation concealment

On registration (visit 1, week −2), participants will be assigned a unique sequential registration number and eligible participants will begin the 2-week run-in phase of the trial to ensure tolerance of compression and remove early healing. On successful completion of the run-phase, eligibility will be reassessed (visit 2, week 0) and consented patients will be randomised by computer in 1:1 ratio to one of the two trial groups using stratified block randomisation with varying block sizes of 2 and 4. Randomisation will be stratified by trial centre and prognostic index (one stratum being either VLU area >5 cm^2 or VLU duration >6 months, the second stratum being both).

The randomisation sequence will be prepared by the trial statistician and loaded into Research Electronic Data Capture (REDCap) databases to be accessed one participant at a time by the research nurse via a computer tablet at the point of randomisation. To complete randomisation, the research nurses must enter data and confirm eligibility for each participant before a treatment assignment is generated via the computer tablet.

Blinding

The participants, research nurses and district nurses will be aware of the participant's allocated treatment. However, outcome assessment for the primary endpoint and a secondary endpoint will be blinded by using an assessor (JW) unaware of treatment allocation to adjudicate healing status (healed/unhealed) of the ulcer from the endpoint photographs. The assessor is a geriatrician with extensive experience in leg ulcer care.

Photographs of the leg and reference ulcer will be taken at baseline and endpoint by the research nurses using a Panasonic Lumix TZ80 with autoflash and macro settings. The baseline photographs will be available to the adjudicator to ensure the same ulcer (or ulcer site) is being reviewed for the endpoint adjudications. The endpoint photographs will be used for the primary endpoint visit

(24 weeks) and the secondary endpoint (visit for time to healing if the reference ulcer heals before or after the 24-week visit). Photographs at baseline and endpoint visits will be uploaded via the internet into OwnCloud folders specific to the site and each participant. OwnCloud is a password-protected cloud storage facility. The photographs will be assessed by the study project manager after each visit to ensure image quality. If image quality is poor, the research nurse will return to the participant to rephotograph the leg and reference ulcer (or ulcer site).

The blinded adjudicator will be notified of new participant photographs requiring assessment, access the OwnCloud participant folder and complete an adjudication form in REDCap on whether the ulcer is healed or unhealed. Where a status cannot be determined from the photograph, the ulcer will be considered unhealed. The adjudicator will not have access to any other forms to ensure blinding is maintained.

On study completion, the Trial Steering Committee (TSC) will interpret study results blinded to treatment allocation and the code broken only after TSC agrees to an interpretation.

Sample size calculation

We estimate 280 participants will be required. A sample size of 252 will be sufficient to show a 20% absolute difference in proportion completely healed at 90% power with an alpha of 0.05 if the control group healing rate for 'slow-healing' VLU is 38% at 24 weeks. This absolute difference is about half the difference suggested in the non-randomised clinical trial conducted on a keratin dressing in China. Despite our previous trials having very high follow-up rates (99% and 100%),[4 16] we have allowed for 10% loss to follow-up, and thus 140 in each group will be required if our assumptions are correct. A sample size of 212 would be sufficient for 80% power using the same assumptions as above.

Baseline data collection

Demographic data collection will include age, sex, self-identified ethnicity, education, employment, height, weight, smoking history, ulcer history (duration, size, number of episodes, type of compression system, clinical history (diabetes, history of deep vein thrombosis, joint replacement, leg fractures, treatments for varicosities) and current medications (table 1).

Primary outcome

The primary outcome is the proportion of patients to have a healed reference ulcer (defined at baseline assessment as the largest VLU where there is more than one VLU) at 24 weeks as adjudicated by the blinded assessor (table 1). Complete healing will be defined as complete epithelialisation of the reference ulcer with absence of scab. The research nurse will visit the participant at 24 weeks and take a photograph of the reference ulcer (or ulcer site if healed). If a scab is present, the research nurses will be instructed to gently remove the scab in order to determine whether there is complete epithelialisation or otherwise.

Secondary outcomes

Secondary outcomes are limited to time to (adjudicated) complete healing, agreement between the blinded and unblinded assessors at 24 weeks, estimated change in ulcer area, change in health-related quality of life and incidence of adverse events (table 1). The process for measurement of time to complete healing will start with notification to the research nurse. When notified by the patient or district nurse of ulcer healing, the research nurse will arrange a visit to photograph the ulcer. The status of the ulcer (healed/unhealed) will be determined by the blinded adjudicator as with the primary outcome. Agreement between the research nurse assessor and the blinded adjudicator on the 24-week healing outcome will be reported. While high levels of agreement have been reported in trials reporting both blinded and open-label outcome assessor, unblinded assessors do overestimate treatment effects.[17] Change in ulcer area will be estimated using a pragmatic approach to ulcer measurement. We do not have the resources to support sophisticated measurement systems, such as Silhouette. The area of an ellipse is closely correlated to actual ulcer area (r=0.95)[18] and from our analysis of data (r=0.92) from a previous trial.[4] Change in health-related quality of life will be assessed using three instruments: two generic instruments (RAND-36, an early version of 36-Item Short Form Survey and EuroQol-5D) and the Charing Cross Venous Ulcer Questionnaire. All three instruments have been used previously in VLU in New Zealand research.[4 19] Adverse events will be reported throughout the follow-up period by either participants or district nurses. An adverse event will be considered any untoward medical event irrespective of whether it is thought to be related to the treatment or not. Adverse events reports will be reviewed by one of the medically qualified co-investigators and coded using the ICD-10-AM (International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification)[20] and study-specific leg ulcer codes.

Statistical analyses

Data analyses will be specified a priori in a statistical analysis plan (SAP) prepared by the trial statistician (and agreed by all members of the TSC). The SAP will be available as a public domain document. Data will be entered into password-secured databases by the research nurse at each study centre. The databases will be REDCap databases hosted at the University of Auckland. REDCap is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages and (4) procedures for importing data from external sources.[21]

Table 1 Standard Protocol Items for Randomised Trials schedule of of enrolment, interventions and assessments

Timepoint	Week –2	Week 0	Week 1 until healing	Week 24 after randomised	If heal before or after week 24
Enrolment					
Eligibility criteria	X	X			
Informed consent	X				
Record or obtain ABI	X				
Measure reference ulcer	X	X			
Photograph reference ulcer		X			
Concomitant medications	X	X		X	X
Run-in phase begins	X				
Background compression	X	X	X	X	X
Run-in phase ends		X			
Allocation		X			
Interventions					
Keratin dressing		X		X	X
Usual care dressing		X		X	X
Assessments					
ABI	X				
Ulcer history	X				
Reference ulcer area	X	X		X	
Clinical history		X			
Reported healing				X	X
Adjudicated healing				X	X
Date of healing					X
Quality of life measures		X		X	
Adverse events*			X	X	X

*Adverse events may be notified to the research nurse at any time during the treatment period by either the participant or the district nurse.
ABI, Ankle Brachial Index.

The data will be extracted into SAS V.9.4 (SAS Institute) for analysis.

All analyses will be carried out on an intention-to-treat basis,[22] with the exception of the health-related quality of analyses. χ^2 tests, relative risks, absolute risks and numbers needed to treat (with 95% CIs) will be calculated for binary outcomes in the first instance, with subsequent multiple logistic regression analysis conducted if necessary to adjust for imbalance in covariates. Sensitivity analyses will be undertaken to determine the impact of missing data. For the main analyses, all participants lost to follow-up will be presumed to have an ulcer that remained unhealed and baseline status will be carried forward. Continuous outcomes (with 95% CIs) will be analysed using multiple linear regression and adjusted for baseline value and other covariates if needed. There will be no imputation of missing data for the health-related quality of life analyses. Any imputation would artificially reduce variability, so only participants who have paired baseline and endpoint data will be included for health-related quality of life analyses. Time-to-event data will be analysed using Kaplan-Meier plots and log-rank test. Cox regression will be used with time-to-event data to take into account known covariates and the varying times since randomisation. The assumption of proportionality will be checked using standard graphical techniques. Adverse events will be analysed using incidence rate ratios.

No interim analyses are planned. Should the keratin dressing prove effective in the primary analysis, heterogeneity of effects on proportion healed will analysed using subgroups specified a priori in the analysis plan. Likely subgroups will be age (quartiles based on the median and IQR), sex (male or female), ethnicity (Māori, Pasifika, non-Māori, non-Pasifika) ulcer size at baseline (<5 cm^2 or >5 cm^2), ulcer duration (<26 weeks or >26 weeks) and prognostic index (score 1 or score 2).

Treatment period and follow-up

After giving consent, all participants will enter into a 2-week run-in phase to assess compliance with compression and initial response to standard care (compression plus non-medicated dressing). Following completion

of the run-in phase, eligibility will be reassessed. Where participants still meet the eligibility criteria and wish to continue in the trial, they will be randomised to receive either a keratin dressing or a usual care dressing. It is anticipated that participants will have on average one dressing change per week, changed each time the compression system is reapplied. A new dressing is to be applied at each dressing change. The allocated treatment will be continued until complete healing or end of the trial (scheduled for 28 February 2019). All care will be delivered by district nurses, with the exception of care delivered during the course of research nurse visits when they will deputise for the district nurse. All participants will be followed up at the scheduled timepoints irrespective of whether they continue with the assigned treatment. The only exception to follow-up will be if the participant requests withdrawal of their data from the trial.

Intervention treatment

The intervention keratin dressing is Keramatrix is available as either a 5×5 cm or a 10×10 cm dressing. Keramatrix, a class IIb device, is manufactured by Keraplast Technologies and has European Community and Food and Drug Administration approvals. The keratin dressing will be applied directly to the ulcer base; where the potential for maceration is considered to of concern, the dressing may be cut to size but otherwise, the usual approach will be to simply lay an unshaped dressing over the ulcer. A secondary dressing may be used for absorbency especially if the preferred method of compression is hosiery or other single layer systems.

Control treatment

The control treatment will be a usual care non-medicated dressing selected from the formulary of dressings available at each study centre. These dressings will include hydrogel, alginate, hydrofibre, polyurethane foam and silicon-impregnated dressings. Other absorbent dressings, for example, combine dressings may also be used as a secondary dressing, especially if the preferred method of compression is hosiery or other single layer systems. The dressing choices will be guided by clinician and/or participant preference.

Background treatments

All participants will receive compression therapy as a background treatment. The choice of compression system will be guided by clinician and/or patient preference and includes the following products: Coban, Coban Lite, Coban Self-adherent, Comprilan, Lastodur, Profore, Profore Lite, Roselastic, Setopress, Surepress and compression hosiery. Throughout the trial, a participant's general practitioner, nurse practitioner or specialist physician will be free to prescribe whatever concomitant treatments are necessary for the appropriate management of their patients. Concomitant medications, including complementary and alternative treatments, supplements and vitamins, will be recorded at each research visit.

Where a participant develops a localised or systemic infection related to the VLU during the course of treatment, the allocated treatment will temporarily cease and the district nurses may use a medicated dressing for the treatment of the infection up to a maximum of 2 weeks. The medicated dressing will selected from the formulary of medicated dressings available at each study centre, including silver-impregnated, iodine-impregnated or honey-impregnated dressings as per clinician and/or participant preference. The participant may also be referred to a general practitioner or nurse practitioner for an antibiotic prescription. Once the infection is resolved, the allocated treatment will be recommenced. Each infection will be considered an adverse event and participants and district nurses will be requested to notify the research nurse.

Adverse events and data safety

In this trial, an adverse event will include any illness, sign, symptom or clinically significant abnormality that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the treatment(s) under trial. All adverse events will be reviewed by a registered medical practitioner who will assess the causal relationship of the adverse event to the dressing materials using WHO causality assessment tool (https://www.who-umc.org/media/2768/standardised-case-causality-assessment.pdf, accessed 10 May 2017).

Serious adverse events (SAEs) will include hospitalisation or prolongation of hospitalisation, life-threatening condition, significant disability or impairment, death, birth defect or any other important medical event. SAEs will be notified to the study project manager as soon as detected and monitored to resolution by the coordinating centre. Any sudden unexpected serious adverse reactions (SUSAR) will be documented and notified to TSC, the Data Safety Monitoring Board (DSMB), the ethics committee and the manufacturer as soon as the coordinating centre is alerted to the SUSAR.

A DSMB has been established to review safety information. The DSMB consists of a senior biostatistician (Chair) and two other University of Auckland staff members with relevant expertise who are not involved with the trial and will meet 6 monthly. The DSMB will draw up their own charter and will be free to review any information or study process in addition to reviewing safety data. The DSMB will make recommendations to the TSC on the continuation of the trial after each meeting or on the notification of a SUSAR.

The trial will be monitored by the project manager (AW). The following information will be audited by the monitor: admission to the district nursing service to verify the patient detail, record of consent, quality of the reference ulcer photographs, key baseline and outcome variables. Monitoring will begin once five participants have been randomised at a study centre.

ETHICS AND DISSEMINATION

The trial has been deemed public good research by the ethics committee and the participants can be covered by the government-funded national no-fault insurance scheme where participants suffer harm from their involvement in the trial. Locality approvals were obtained from each of organisations responsible for the participating study centres prior to the trial start on 1 March 2017. Changes to the protocol are sought as required, incorporated into the trial registration as appropriate once notification of approval has been received, and communicated to the site investigators and research nurses.

We will publish the results of this trial in reputable journal within 1 year of completing follow-up. The results will be notified to the participants on trial completion. The data and materials (patient information sheet and informed consent form, study protocol, manual of procedures, study forms and SAP) will be available on application to the corresponding author and we welcome requests for information and/or data sharing.

TRIAL STATUS

Recruitment to the trial commenced in the five study centres in March 2017; 89 participants had been registered and 73 participants randomised by 23 November 2017. The trial is registered on ClinicalTrials.gov (NCT02896725), a WHO compliant public domain trials register. The trial has a Universal Trial Number obtained from WHO (U1111-1186-5202).

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Contributors AJ is the principal investigator, led all stages of the design development, grant application and protocol development. AJ drafted the manuscript. AW, CB, VP and JW all contributed to the study design, grant application and protocol development. All authors edited the draft manuscript and approved the manuscript for submission.

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Disclaimer Neither the Health Research Council nor Keraplast Technologies have any role in the conduct and analysis of the trial nor will they have any role in the interpretation or decision to publish the findings from the trial.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Ethical approval for the trial was obtained on 21 September 2016 from the Northern A Health and Disability Ethics Committee (Reference 16/NTA/142) by the trial coordinating centre (National Institute for Health Innovation).

Provenance and peer review Not commissioned; externally peer reviewed.

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