

VenUS 6 – A randomised controlled trial of compression therapies for the treatment of venous leg ulcers: Study design and update

Sabeen Zahra PhD¹, Catherine Arundel MSc¹, Katherine Jones PhD¹, Tom Davill MSc¹, Gareth Roberts BSc¹, Jo Dumville PhD²,
on behalf of the VenUS 6 trial team

¹York Trials Unit, Department of Health Sciences, Faculty of Science, University of York, YO10 5DD

²Division of Nursing, Midwifery and Social Work, Jean McFarlane Building, University of Manchester, Oxford Road, Manchester, M13 9PL

Correspondence: Catherine.arundel@york.ac.uk · Conflict of interests: None

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ABSTRACT

Background

Venous leg ulcers (VLU) are common wounds, mainly in the gaiter region of the leg. Compression therapy is an effective treatment for reducing the time to healing of VLU. The four-layer bandage and two-layer hosiery protocols are supported by good evidence for clinical and cost effectiveness. There is more limited evidence for other treatments, such as the two-layer bandage and compression wraps. Robust evidence is required to compare the clinical and cost effectiveness of these and to investigate which is the best compression treatment for reducing time to healing of VLU whilst offering value for money.

Aim

VenUS 6 aims to investigate the clinical and cost effectiveness of evidence-based compression, two-layer bandage and compression wraps for time to healing of VLU.

Method

This multicentre, pragmatic, three-arm parallel group study aims to recruit 675 eligible participants aged ≥ 18 years with at least one VLU, and who can tolerate full compression and give written consent. Participants are allocated 1:1:1 to receive

evidence-based compression, two-layer bandage or compression wrap. Participants are followed up with weekly assessments until the participant's reference leg is ulcer-free and no further nursing assessments are required to treat the leg. Reference ulcer healing is confirmed by a healthcare professional/treating nurse. Participant-reported outcomes are collected at baseline and at 1, 3, 6 and 12 months. The primary outcome is time to healing of the reference ulcer. Secondary outcomes include clinical events and participant-reported ulcer related pain, quality of life, treatment adherence and resource use.

INTRODUCTION

Venous leg ulcers (VLU) are common, recurring open wounds on the lower leg resulting from venous insufficiency. Wound care is mainly delivered in community-based clinics, patient homes or outpatient settings. Delivering effective treatments remains important to maximise ulcer-free days and improve the health-related quality of life of people with VLU. Evidence suggests full (high) compression treatment, aiming to deliver around 40mmHg compression at the ankle, is effective for reducing ulcer healing time and is cost effective.¹ More recently, the Early Venous Reflux Ablation (EVRA) trial has reported the early provision of endovenous ablation surgery to further reduce time to healing and

to be cost effective.^{2,3} Due to the long waiting times for surgery referrals, however, such treatment may be delayed, resulting in people receiving compression therapies in the interim. Furthermore, some people with VLU might not be eligible for this surgery and so would require compression therapy as their primary treatment. Understanding the most clinically and cost-effective compression treatment for VLU remains an important aim in wound care.

The main full compression treatments currently in use in the UK's National Health Service (NHS) are: 1) two-layer hosiery or the four-layer bandage (termed here as 'evidence-based compression', or EBC), 2) the two-layer bandage and 3) compression wraps. The effectiveness of EBC therapies was assessed previously with the four-layer bandage and shown to be more clinically and cost effective than the short stretch bandage.⁴ A subsequent trial with 457 participants showed little difference in healing times between the four-layer bandage and two-layer hosiery.^{5,6} Two-layer hosiery was also found to be a cost effective treatment compared with the four-layer bandage, although this treatment is not suitable for all patients.

There is more limited evidence for other compression therapies. Three trials involving a total of 299 participants have compared two-layer with four-layer bandages, with uncertainty around the relative effects of the two treatment options.⁷⁻⁹ For compression wraps, only one small trial has been reported (24 participants), with a relatively short follow-up period of 12 weeks. Time to healing or complete wound healing was not reported.¹⁰ Whilst the relative effectiveness evidence is limited, two-layer bandages and, increasingly, compression wraps are widely used as treatments for VLU. The generation of further robust evidence through a sufficiently powered randomised controlled trial to evaluate which is the best full compression treatment for reducing time to healing for VLU can inform future decision making in this area.

Given the varying evidence for different compression systems, the VenUS 6 study has been designed to undertake the following comparisons for time to healing of VLU and address the uncertainties identified above in a way that is most relevant to decision makers. The key objectives are, therefore:

- To compare compression wraps with EBC in terms of the time to healing of VLU;
- To determine whether two-layer bandages are non-inferior to EBC for time to healing of VLU; and
- To determine which is the most cost effective, full compression treatment for VLU.

METHODS

Trial design

VenUS 6 is a multicentre, three-arm, parallel group, pragmatic randomised controlled trial evaluating the clinical and cost effectiveness of EBC, two-layer bandages and compression wraps. The trial has a 32-month recruitment period, including an initial 6-month internal pilot. Follow up will be variable, with participants followed for minimum of 4 months and a maximum of 12 months, following randomisation. This is a pragmatic trial and so, following randomisation and application of the allocated treatment, each participant will receive treatment as per routine clinical practice. The trial is registered with ISRCTN (reference: 67321719) and approved by the Research Ethics Committee (reference: 20/WS/0121), Health Research Authority and Health and Care Research Wales (HCRW). It is funded by the National Institute Health and Research Health Technology Assessment programme (NIHR128625) and sponsored by the Manchester University NHS Foundation Trust.

Study setting

The study will enlist up to 35 sites, including secondary care NHS trusts, community NHS trusts and primary care centres.

Participants: We will recruit adult (≥ 18 yrs) participants with at least one VLU. Patients will be eligible for inclusion if they have least one VLU wholly or partially within the gaiter region of the leg; have an ankle brachial pressure index of ≥ 0.8 taken within last 3 months, or any locally approved alternate assessment to rule out peripheral arterial disease; and if they are able to tolerate full compression. Participants will be excluded if they: have a VLU that has non-venous aetiology and is confined to the foot only, are an active participant in another study evaluating treatments for VLU, have already been a VenUS 6 participant or if they have a planned treatment to re-

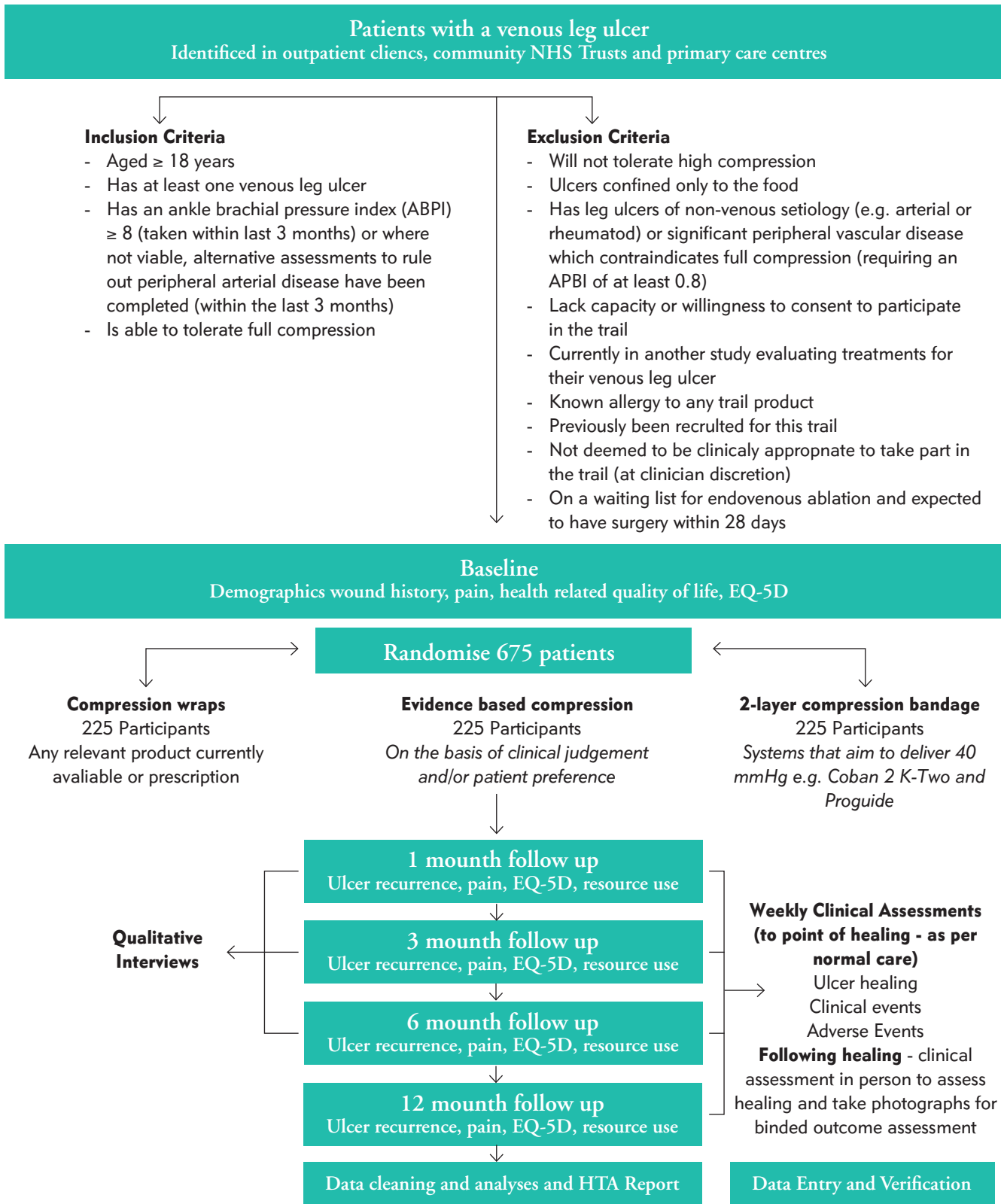


Figure 1: VenUS 6 design/participant pathway throughout the study

move/close superficial veins within the next 28 days.
Figure 1 shows the VenUS 6 study design.

Randomisation and allocation

In all, 675 eligible participants will be equally randomised and allocated to one of the three

compression therapies. A secure, centralised, online randomisation service hosted by the University of York Trials Unit will be used to randomise eligible participants. Randomisation will be stratified by ulcer duration (\leq 6 months or $>$ 6 months) and ulcer area (\leq 5cm² or $>$ 5cm²) using permuted blocks.

Interventions

A total of 225 participants will be received into each of the following three intervention arms:

1. Evidence-based compression:

This is the choice arm for applying a four-layer bandage or two-layer compression hosiery system based on clinical discretion or participant preference. Any recognised brand of four-layer bandage can be used if it aims to deliver ≥ 40 mmHg compression at the ankle. Compression hosiery consists of two layers of compression aiming to deliver graduated, sustained compression of ≥ 40 mmHg at the ankle. The first layer is an understocking or liner, over which a second layer/overstocking is applied.

2. Two-layer bandage:

This contains an initial bandage layer covered with a top cohesive layer bandage to apply ≥ 40 mmHg compression at the ankle. Any recognised two-layer system listed under the British National Formulary as a 'multilayer compression bandaging/two-layer system' may be used.¹¹

3. Compression wrap:

Compression wraps are defined as using hook and loop systems (such as Velcro) to secure the compression sleeve around the foot and leg. Wraps may be used in VenUS 6 if they are designed to be worn on the lower leg and foot, aim to deliver ≥ 40 mmHg compression at the ankle and are CE marked and available on FP-10. These may be used with a compressive or non-compressive liner.

Outcomes:

The primary outcome of the trial is time to healing of the reference ulcer, defined as complete epithelial cover in the absence of a scab (eschar) with no dressing required. We will undertake a blinded outcome assessment by assessing images of VLU taken at baseline and once per week for four weeks following healing. Secondary outcome measures are ulcer recurrence, adverse events, health-related quality of life, resource use, wound-related pain, treatment adherence and ease of use. These will be collected through study-specific case report forms. Data on treatment use; clinical events, including the healing of the VLU; and adverse events will be collected during nurse assessments until the participant's leg is ulcer-free, and via monthly telephone contact following healing until the end of the participant's follow up period. During the trial, participants will also be asked

to complete postal questionnaires sent at months 1, 3, 6 and 12, following randomisation, to collect information regarding quality of life, pain, treatment adherence and resource use in relation to VLU. We will integrate VenUS 6 into a wider economic model to explore the relative cost effectiveness of alternative compression treatments.

VenUS 6 progress update:

Sites update:

To date, 18 sites have been opened and are actively recruiting participants to VenUS 6. This includes: 12 secondary care trusts, 4 community trusts and 2 GP practices. In addition, there are 12 sites currently in the process of being set up for the study. Full support is provided to sites during the set-up process and to help in delivering VenUS 6 study activities locally. There is also a per-participant fee of £469 available to sites to support the study's activities.

Recruitment update:

Recruitment to VenUS 6 commenced on 3 February 2021 and is anticipated to be completed by 30 March 2023. As of 31 January 2022, 155 participants (23% of 675) had been recruited. For information related to VenUS 6 progress updates, please visit the VenUS 6 webpage at:

<https://www.york.ac.uk/healthsciences/research/trials/research/trials/venus6/#tab-3>

VenUS 6 is still open to new recruiting sites. For more information and to express interest in participating, please contact: venus6-trial-group@york.ac.uk

Declarations

Competing interests

All authors declare that they have no competing interests.

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not necessarily those of the NIHR or the Department of Health and Social Care.

Availability of data and materials

Datasets and statistical code used in this study will be available from the corresponding author, on reasonable request, following completion of the trial.

Ethics approval and consent to participate

Ethical approval for this trial has been granted by the West of Scotland Research Ethics Committee 4 – reference 20/WS/0121 (approval date: 15.09.2020). Participants are required to provide informed consent prior to participation.

Consent for publication

Not applicable.

KEY MESSAGES

- Full compression therapy options have been found to be the first-line treatment for venous leg ulcers (VLU) and are routinely used across the UK's NHS. Despite this, identification of the most effective full compression therapy treatments remains important.
- VenUS 6 aims to evaluate the clinical and cost effectiveness of current compression therapies, evidence-based compression (four-layer bandage or two-layer compression hosiery), two-layer bandage and compression wraps, in terms of time to healing of venous leg ulcers.
- VenUS 6 is currently in progress and is looking for more sites to participate in recruiting participants to the study. For more information and to express an interest please, contact venus6-trial-group@york.ac.uk. ■

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