

VenUS III: a randomised controlled trial of therapeutic ultrasound in the management of venous leg ulcers

JM Watson, AR Kang'ombe, MO Soares, L-H Chuang, G Worthy, JM Bland, C Iglesias, N Cullum, D Torgerson and EA Nelson, on behalf of the VenUS III team



March 2011
10.3310/hta15130

Health Technology Assessment
NIHR HTA programme
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Declaration of competing interests: none

Published March 2011

DOI: 10.3310/hta15130

This report should be referenced as follows:

Watson JM, Kang'ombe AR, Soares MO, Chuang L-H, Worthy G, Bland JM, *et al.* VenUS III: a randomised controlled trial of therapeutic ultrasound in the management of venous leg ulcers. *Health Technol Assess* 2011;**15**(13).

Health Technology Assessment is indexed and abstracted in *Index Medicus/MEDLINE*, *Excerpta Medica/EMBASE*, *Science Citation Index Expanded (SciSearch®)* and *Current Contents®/Clinical Medicine*.

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 02/37/03. The contractual start date was in May 2005. The draft report began editorial review in December 2009 and was accepted for publication in July 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

ISSN 2046-4932 (DVD)

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Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.
 Printed on acid-free paper in the UK by the Charlesworth Group.

Abstract

VenUS III: a randomised controlled trial of therapeutic ultrasound in the management of venous leg ulcers

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Objectives: To compare the clinical effectiveness and cost-effectiveness of low-dose ultrasound delivered in conjunction with standard care against standard care alone in the treatment of hard-to-heal venous ulcers.

Design: A multicentre, pragmatic, two-armed randomised controlled trial with an economic evaluation.

Setting: Community nurse services; community leg ulcer clinics; hospital outpatient leg ulcer clinics, among both urban and rural settings in England, Scotland, Northern Ireland and Ireland.

Participants: Patients with a venous leg ulcer of >6 months' duration or >5 cm² and an ankle-brachial pressure index of ≥ 0.8 . In total, 337 patients were recruited to the study.

Interventions: Participants in the intervention group received low-dose ultrasound (0.5 W/cm²) delivered at 1 MHz, pulsed pattern of 1:4, applied to periulcer skin (via a water-based contact gel) weekly for up to 12 weeks alongside standard care. Standard care consisted of low-adherent dressings and compression therapy, renewed as recommended by the patient's nurse and modified if required to reflect changes in ulcer and skin condition. The output of the ultrasound machines was checked every 3 months to confirm intervention fidelity.

Main outcome measures: The primary end point was time to healing of the largest eligible ulcer (reference ulcer). Secondary outcomes were time to healing of all ulcers, proportion of patients healed, percentage and absolute change in ulcer size, proportion of time patients were ulcer free, cost of treatments, health-related quality of life (HRQoL), adverse events, withdrawal and loss to follow-up.

Results: There was a small, and statistically not significant, difference in the median time to complete ulcer healing of all ulcers in favour of standard care [median 328 days, 95% confidence interval (CI) 235 days, inestimable] compared with ultrasound (median 365 days, 95% CI 224 days, inestimable). There was no difference between groups in the proportion of patients with ulcers healed at 12 months (72/168 in ultrasound vs 78/169 standard care), nor in the change in ulcer size at 4 weeks. There was no evidence of a difference in recurrence of healed ulcers. There was no difference in HRQoL [measured using the Short Form questionnaire-12 items (SF-12)] between the two groups. There were more adverse events with ultrasound than with standard care. Ultrasound therapy as an adjuvant to standard care was found not to be a cost-effective treatment when compared

with standard care. The mean cost of ultrasound was £197.88 (bias-corrected 95% CI –£35.19 to £420.32) higher than standard care per participant per year. There was a significant relationship between ulcer healing and area and duration at baseline. In addition, those centres with high recruitment rates had the highest healing rates.

Conclusions: Low-dose ultrasound, delivered weekly during dressing changes, added to the package of current best practice (dressings, compression therapy) did not increase ulcer healing rates, affect quality of life (QoL) or reduce recurrence. It was associated with higher costs and more adverse events. There is no evidence that adding low-dose ultrasound to standard care for ‘hard-to-heal’ ulcers aids healing, improves QoL or reduces recurrence. It increases costs and adverse events. The relationship between ulcer healing rates and patient recruitment is worthy of further study.

Trial registration: Current Controlled Trials ISRCTN21175670.

Funding: This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 15, No. 13. See the HTA programme website for further project information.

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List of abbreviations

ABPI	ankle–brachial pressure index
A_{ER}	effective radiating area
BNF	<i>British National Formulary</i>
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
df	degrees of freedom
EQ-5D	European Quality of Life-5 Dimensions
GP	general practitioner
HbA _{1c}	glycated haemoglobin
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IPW	inverse probability weight
ISRCTN	International Standard Randomised Controlled Trial Number
LRIC	Local Research Ethics Committee
MCS	mental component score
MREC	Multicentre Research Ethics Committee
NICE	National Institute for Health and Clinical Excellence
NPL	National Physical Laboratory
NSAE	non-serious adverse event
PCS	physical component score
PH	proportional hazard
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
SAE	serious adverse event
SD	standard deviation
SF-12	Short Form questionnaire-12 items
VAS	visual analogue scale
VenUS	Venous Ulcer Study
WHSCCT	Western Health and Social Care Trust

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Objectives

To compare the clinical effectiveness and cost-effectiveness of low-dose ultrasound delivered in conjunction with standard care against standard care alone in the treatment of hard-to-heal venous ulcers.

Methods

Design

A multicentre, pragmatic, parallel, two-armed randomised controlled trial with an economic evaluation. Allocation was concealed, treating nurses and patients were aware of allocation, and outcome assessment was by treating-nurse report confirmed by blinded review of photographs at healing and 7 days later.

Setting

Community nurse services; community leg ulcer clinics; hospital outpatient leg ulcer clinics, among both urban and rural settings in England, Scotland, Northern Ireland and Ireland.

Participants

Patients were eligible to participate in the trial if they presented with a venous leg ulcer of > 6 months' duration or > 5 cm² and an ankle-brachial pressure index of ≥ 0.8 .

Interventions

Participants in the intervention group received low-dose ultrasound (0.5 W/cm²) delivered at 1 MHz, pulsed pattern of 1:4, applied to periulcer skin (via a water-based contact gel) weekly for up to 12 weeks alongside standard care. Standard care consisted of low-adherent dressings and compression therapy, renewed as recommended by the patient's nurse and modified if required to reflect changes in ulcer and skin condition. The ultrasound machines output was checked every 3 months to confirm intervention fidelity.

Main outcome measures

The primary end point was time to healing of the largest eligible ulcer (called the reference ulcer). Secondary outcomes were: time to healing of all ulcers, proportion of patients healed, percentage and absolute change in ulcer size, proportion of time patients were ulcer free (incorporating recurrence rates), cost of treatments, health-related quality of life (HRQoL), adverse events, withdrawal and loss to follow-up. Cost-effectiveness and cost-utility analyses were also undertaken alongside the trial.

Results

There was no statistically significant difference in the time to healing of the reference leg ulcer between the two groups (log-rank statistic 0.2544, $p = 0.6140$). The median time to reference leg ulcer healing was inestimable. There was a small, and statistically not significant, difference in the median time to complete ulcer healing of all ulcers in favour of standard care [median 328 days, 95% confidence interval (CI) 235 days, inestimable] compared with ultrasound (median

365 days, 95% CI 224 days, inestimable). There was no statistically significant difference between groups in the proportion of patients with ulcers healed at 12 months (72/168 in ultrasound vs 78/169 standard care, Fisher's exact test, $p=0.3854$), nor in the change in ulcer area at 4 weeks. There was no evidence of a difference in recurrence of healed ulcers and few people had a recurrence within trial follow-up.

There was no difference in HRQoL [measured using the Short Form questionnaire-12 items (SF-12)] between the two groups. There were more adverse events with ultrasound than with standard care, and those events reported were consistent with those observed in other leg ulcer trials. Ultrasound therapy as an adjuvant to standard care was found not to be a cost-effective treatment when compared with standard care. The mean cost of ultrasound was £197.88 (bias-corrected 95% CI -£35.19 to £420.32) *higher* than standard care per participant per year. There was a significant relationship between ulcer healing and area and duration at baseline. In addition, those centres with high recruitment rates had the highest healing rates. The number of adverse events was significantly associated with the treatment received, with more episodes in the ultrasound group than in the standard care group. This large trial failed to find any evidence that ultrasound aided healing in this group, in contrast to earlier, smaller studies with methodological weaknesses and less effective standard care. We cannot exclude the possibility that ultrasound at other regimens might be effective, but the present evidence for ultrasound, based on the total available evidence, is not suggestive of any effects.

Conclusions

Low-dose ultrasound, delivered weekly during dressing changes, added to the package of current best practice (dressings, compression therapy), did not increase ulcer healing rates, affect quality of life (QoL) or reduce recurrence in people with hard-to-heal ulcers. Ultrasound was associated with higher costs and more adverse events. We did, however, confirm earlier findings that baseline ulcer area and ulcer duration were statistically significant predictors of time to healing, with larger ulcers and those of a longer duration taking longer to heal.

Implications for health care

There is no evidence that adding low-dose ultrasound, delivered weekly for 12 weeks, to standard care for 'hard-to-heal' ulcers aids healing, improves QoL or reduces recurrence. It increases costs and the number of adverse events.

Recommendations for future research

We identified a large variation in healing rates according to trial centres, with those centres recruiting more patients to the trial having higher healing rates overall. We controlled for ulcer area and duration; hence, the difference in healing rates across centres is not likely to be due to these prognostic factors being distributed differently across sites (i.e. larger/old ulcers in one site). The relationship between ulcer healing rates and patient recruitment is worthy of further study.

Study registration

This trial is registered as ISRCTN21175670.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1

Background

Venous leg ulcers

Leg ulceration is a chronic, recurring condition, affecting 15–18/1000 adults in industrialised countries,¹ with venous leg ulcers representing up to 84% of all leg ulcer cases in developed countries.² Venous insufficiency occurs when the foot or calf muscle pumps are unable to empty the veins effectively, causing the pressure within the veins and capillaries to rise above normal limits.³ This raised pressure leads to numerous changes in the capillaries and surrounding tissues, manifested by signs and symptoms such as venous flare, oedema, and hardening and staining of the dermal tissue (lipodermatosclerosis), the progressive stages of which can eventually lead to ulceration.⁴ These ulcers have a significant personal impact on health and quality of life (QoL).^{2,5}

Treating venous leg ulcers

The only therapy so far shown to be clearly effective in the treatment of venous leg ulcers is the application of compression therapy, as either bandaging or hosiery, with high compression (around 40 mmHg pressure at the ankle) being more effective than lower levels of compression [relative risk of healing 1.5, 95% confidence interval (CI) 1.2 to 2.0].⁶ We know from both trials of compression therapy and other prognostic studies that small ulcers [$< 5 \text{ cm}^2$ in area] and new ulcers (< 6 months in duration) treated with high compression heal quickly. For example, in a large trial of compression bandaging the median time to healing of ulcers with pre-trial duration of < 6 months was 77 days.⁷ New ulcers treated with high compression, therefore, can be described as generally healing *without* the need for adjuvant therapies. One high-quality prognostic study has found that 95% of venous ulcers that are *both* small ($< 5 \text{ cm}^2$ in area) *and* new (< 6 months in duration), if treated with high compression, can be expected to heal within 6 months (95% CI 75% to 99%).⁸ Audits of healing times using four-layer high compression (widely used in the UK) confirm the importance of ulcer area and duration in predicting healing at 6 months.^{9,10} One of the remaining clinical challenges is how to increase healing in those ulcers that are not 'easy to heal' (i.e. the big/old ulcers rather than the small/new ulcers). The goal is both to increase the proportion of ulcers healed (20% remained unhealed in a large bandaging trial at 12 months)⁷ *and* to decrease the time to healing among people with longstanding ulceration or large ulcers.

Cost of venous leg ulceration

Leg ulceration is a condition associated with large financial costs to health-care providers. The cost of leg ulcer management in the UK in 1989 was estimated to be between £150M and £600M per annum, with $> 60\%$ of this cost attributed to community-based nursing services.¹¹ Recent studies have estimated the annual cost of treating a venous leg ulcer patient as being approximately £700–900, which increases the longer it takes for the ulcer to heal or the larger it becomes.^{12,13} The 2004 Healthcare Commission estimated that NHS leg ulcer treatments cost £300–600M per annum and wound dressings accounted for 5 million community prescriptions in England during 2006 at a cost of £122M.¹⁴ With the majority of leg ulcer patients in the UK treated within the community,¹⁵ such patients often constitute a large proportion of community nurses' caseloads.¹⁶

Therapeutic ultrasound

Ultrasound therapy is a well-recognised treatment option for soft tissue injuries in the physiotherapy clinic, but has been more recently used in some specialist centres for the management of chronic wounds.³

Mechanical vibrations transmitted at a frequency > 20,000 Hz are above the level of human hearing and are known as ultrasonic.¹⁷ Ultrasound may be divided into two classes: those using 'high' intensities (> 3 W/cm²), used for ultrasonic scalpels, and those using 'low' intensities (up to 3 W/cm²), used to stimulate normal physiological responses to injury to aid repair.¹⁸ The type of ultrasound used is dependent on the target tissues (structure and depth) and the intended effect (i.e. heating the tissues or not). Tissues with a higher protein content (e.g. ligament and tendon) are able to absorb ultrasound to a greater extent than those with a low protein content (e.g. blood and fat).¹⁹ Therapeutic ultrasound has a frequency of 0.75–3.00 MHz, and most machines used to deliver it are set at a frequency of either 1 or 3 MHz.²⁰ The absorption coefficient of ultrasound in soft tissue increases linearly with frequency, so using higher frequencies (say 3 rather than 1 MHz) reduces the penetration depth by about one-third (from 37 to 12 mm in skin).²¹

Presumed mechanisms of action

There are two types of mechanisms commonly thought to explain the effects produced by therapeutic ultrasound, and these are classed as thermal and non-thermal effects,¹⁸ although ter Haar¹⁸ and Baker *et al.*²¹ argue that both effects may be present to varying degrees. They agree that it is difficult to identify the mechanisms involved, let alone separate the thermal and non-thermal effects. Investigators have described the effects of ultrasound on tissues *in vitro* and *in vivo*, but it is not clear whether these are responsible for reported clinical effects, or merely incidental.

Many physiological responses to the biophysical effects of therapeutic ultrasound have been described, and the research has been reviewed by Baker *et al.*²¹ and others.^{18,20}

When ultrasound travels through tissue, a percentage of it is absorbed, which leads to the generation of heat within the tissue.¹⁹ The beneficial effects thought to arise from this heating include an increase in blood flow, reduction in muscle spasm, increased extensibility of collagen fibres and a proinflammatory response.²⁰ Any problem of excess heat is reduced by using pulsed ultrasound (which has an on/off cycle), as the effective intensity is lower, with the heat being dissipated between the pulses.²² While ultrasound has historically been used primarily for its professed thermal effects, it is suggested that 'non-thermal' mechanisms play a role in producing therapeutic effects.¹⁹ Watson¹⁹ concludes that although the therapeutic benefits of tissue heating are well known, the ability of ultrasound to generate sufficient thermal change in tissues to achieve these effects is doubtful.

Purported non-thermal mechanisms are predominantly attributed to 'cavitation' – the production and vibration of micron-sized bubbles within the tissue fluids which, as the bubbles move and oscillate within the fluids, can cause changes in the cellular activities of the targeted tissues.¹⁷ An additional outcome of ultrasound is 'acoustic streaming', which is described as the 'localised liquid flow in the fluid around the vibrating bubble.'²² Baker *et al.*,²¹ however, argue that there is no evidence from *in vivo* studies in humans that cavitation occurs at the ultrasound doses used for tissue repair. Given the absence of cavitation, except in gas-filled cavities (such as the lungs), it is further argued that acoustic streaming does not occur *in vivo*. The way in which cavitation or acoustic streaming might contribute to tissue repair is not obvious, but it is postulated that they might lead to a reversible increase in cell membrane permeability and increased protein synthesis.¹⁷

Ultrasound application

Ultrasound is reflected at the skin, as the air–skin interface presents a barrier to the transmission of ultrasound; thus, it is necessary to provide a coupling medium to allow the ultrasound to be transmitted into the tissues.¹⁹ Suitable coupling mediums include gel with a high water content, a film dressing, water or saline.¹⁷

The dose at which ultrasound is delivered is related to its frequency (Hz), power (W/cm^2), duty cycle (pulsed or continuous) and the duration of treatment, which produce a large number of possible combinations.¹⁹

Ultrasound is contraindicated in people with ankle prostheses/metal anywhere in the foot (e.g. pin and plate, shrapnel), because both metal and the bone cement used in the replacement of joints have a high absorption capacity. The application of ultrasound to the ankle area may lead to heat damage of the local area and any prosthetic joints.²³ Ultrasound is also contraindicated for people with suspected thrombophlebitis (the mechanical vibrations may cause an embolism), people with active cellulitis (potential risk of accelerated growth and dissemination of bacteria throughout the body), in cases of suspected or confirmed local cancer/metastatic disease and in cases of obvious ulcer infection.²³

Existing evidence for the effect of ultrasound on healing

A number of studies have investigated the impact of ultrasound on skin cells (in vitro) and chronic wounds (in vivo). In general, there have been few good-quality studies demonstrating that any of the 'in vitro' effects have any clinical importance.²¹

Before designing this trial we were aware of seven trials^{24–30} of ultrasound for treating venous leg ulcers, and one³¹ became available during this period (*Table 1*). These were summarised in a systematic review.³² The sample sizes in these trials ranged from 12 to 108 patients, and four trials^{25,26,28,29} used true randomisation with allocation concealment. The trials made various comparisons of ultrasound versus sham (four trials^{24–27}) or ultrasound as an adjunct to standard care versus standard care alone. Various types of ultrasound at different dose were used. Frequency of ultrasound ranged between 0.03 and 3 MHz: 0.03 MHz was used in two trials^{28,30} (applied via a water bath), 1 MHz was used in four trials^{24,25,29,31} and 3 MHz was used in another two trials^{26,27} (1 MHz has greater depth penetration than 3 MHz). Ultrasound doses ranged between 0.1 and 1.0 W/cm^2 . In two trials^{28,30} in which a water bath ultrasound device was used, 0.1 W/cm^2 was used. Doses of 0.5 W/cm^2 were used in three trials^{25,29,31} and 1.0 W/cm^2 in four trials^{24,26,27,31} (one trial³¹ compared both 0.5 and 1 W/cm^2 against standard care). In the seven trials available during the study design phase the following therapeutic regimens were used:

- One²⁴ reported an evaluation of ultrasound at 1 MHz and 1.0 W/cm^2 (38 people).
- Two^{28,30} reported evaluations of ultrasound with a water bath at 30 kHz and 0.1 W/cm^2 (61 people).
- Two^{26,27} reported evaluations of ultrasound at 3 MHz and 1.0 W/cm^2 (53 people).
- Two^{25,29} reported evaluations of ultrasound at 1 MHz and 0.5 W/cm^2 (152 people).

Given that the most evidence was available for the combination of ultrasound at 1 MHz and 0.5 W/cm^2 , and this included the study with only moderate risk of bias, we decided to use this regimen for the trial. No trials reported that they confirmed ultrasound equipment output.

The largest trial²⁹ (108 people) evaluated ultrasound administered weekly, but the other trials administered ultrasound two or three times a week, with one²⁵ having a reducing frequency from

TABLE 1 Trial of ultrasound for venous ulcers prior to VenUS III study design

First author of trial (number in trial)	Comparison (sham/standard care)	Ultrasound regimen (frequency/dose)	Times per week	Duration of each treatment (minutes)	Period of ultrasound therapy (weeks)
Eriksson ²⁴ (<i>n</i> = 38)	Sham	1 MHz/1.0W/cm ²	Two	10	8
Lundeberg ²⁵ (<i>n</i> = 44)	Sham	1 MHz/0.5W/cm ²	Three, two, one	10	12
Roche ²⁶ (<i>n</i> = 26)	Sham	3 MHz/1.0W/cm ²	Three	?	4
Dyson ²⁷ (<i>n</i> = 25)	Sham	3 MHz/1.0W/cm ²	Three	10	4
Weichenthal ²⁸ (<i>n</i> = 37)	Standard care	0.3 MHz/0.1W/cm ²	Three	10	8
Callam ²⁹ (<i>n</i> = 108)	Standard care	1 MHz/0.5W/cm ²	One	5–10	12
Peschen ³⁰ (<i>n</i> = 12)	Standard care	0.3 MHz/0.1 W/cm ²	Three	3	12

?, not reported.

three to one time(s) a week. Four trials^{25,29–31} used ultrasound for 12 weeks, two^{24,28} for 8 weeks and two^{26,27} for 4 weeks. The five trials that described duration of ultrasound regimen used 10 minutes (three trials^{24,28,30}) or 5–10 minutes, depending on ulcer area (two trials^{26,27}).

The heterogeneity of these trials with respect to the delivery mode, dose, duration, treatment length and frequency used means that meta-analysis of all these trials may not be reliable. Another problem with synthesising these studies is the likely difference in the ultrasound actually delivered, even when treatment regimens appear similar, owing to the differences in output between machines and over time (drift). Not all these trials restricted their recruitment to people with ‘hard-to-heal ulcers’ and some were performed without high-compression therapy as the standard care system; hence, their applicability to current care challenges faced by clinicians is unclear. Given that standard care of venous ulcers, using high compression and simple dressings, heals around 80% of all ulcers within 12 months, ultrasound as an adjuvant therapy is likely to be reserved for those resistant to standard therapy, or whose ulcers are identified at the outset as ‘hard-to-heal’.

The Cochrane review³² concluded that there was tentative evidence that ultrasound increased the healing of venous ulcers, but that the trials identified had moderate to high risk of bias. The reviewers, therefore, called for a large, methodologically robust trial of ultrasound to be undertaken; hence, we set out to determine whether adding ultrasound to best practice for venous ulcers (appropriate compression therapy) increased the chance and rate of healing.

Summary of main points

The majority of venous leg ulcers heal in 6–12 months, but those with a duration of >6 months, or which are larger than average, are harder to heal. With the best available standard care – simple dressings and high-compression bandages – these ‘harder to heal’ ulcers usually take >6 months to heal. With the burden, in terms of both patients’ finances and QoL, attributed to leg ulcers being significant, increasing the numbers of ulcers healing and decreasing the time taken for ulcers to heal is important.

Ultrasound has been used for many years to help tissue repair and it is commonly given by physiotherapists to help joint and muscle repair, using ultrasound treatment regimens of treatment three to seven times a week. It is not feasible to administer ultrasound with this frequency when treating venous ulcers in the community as delivering ultrasound to an ulcer

can be done only when bandages are removed, for example during regular dressing changes. Compression bandages stay in place for up to a week and current thinking about wound healing suggests that wounds should be disturbed as little as possible to avoid damaging delicate tissues at each dressing change. The costs of having daily appointments with the nurse for dressing changes for the purpose of administering ultrasound is likely to be prohibitive (even if nurse workload allowed daily dressings for this purpose, which is unlikely).

There is some evidence that delivering ultrasound to the wound can help heal leg ulcers, although the previous studies were methodologically weak, small in size and varied widely in application regimens, and not all used high-compression therapy as standard care. In addition, the previous trials included people with small, new ulcers, which heal relatively quickly using compression bandaging, and therefore the results of these studies may not be applicable to 'hard-to-heal' ulcers.

Research objectives

To compare the clinical effectiveness and cost-effectiveness of low-dose ultrasound (0.5 W/cm² spatial average and temporal peak) delivered at 1 MHz in conjunction with standard care against standard care alone in the treatment of hard-to-heal venous ulcers.

Primary objective

- To compare the effects of low-dose ultrasound plus standard care with standard care alone on the time to healing of the reference (largest) ulcer.

Secondary objectives

- To compare the cost-effectiveness of ultrasound plus standard care with standard care alone.
- To compare the effects of ultrasound plus standard care with standard care alone on the proportion of patients with ulcers healed at 12 months.
- To compare the effects of ultrasound plus standard care with standard care alone on percentage and absolute change in ulcer size.
- To compare the effects of ultrasound plus standard care with standard care alone on health-related quality of life (HRQoL).
- To compare the effects of ultrasound plus standard care with standard care alone on reported adverse events, withdrawals and loss to follow-up.
- To compare the effects of ultrasound plus standard care with standard care alone on the proportion of time patients are ulcer free.

Chapter 2

Methods

Trial design

The Venus Ulcer Study (VenUS) III trial was a pragmatic, multicentre, two-armed, randomised controlled, open trial with equal randomisation. Participants with 'hard-to-heal' ulcers (>6 months' duration and/or larger than 5 cm²) were randomised (1 : 1) to receive either:

- low-dose (0.5 W/cm²) ultrasound, 1 MHz, and a pulsed pattern of 1 : 4 weekly for up to 12 weeks, plus standard care, or
- standard care alone.

The study protocol can be seen in *Appendix 1*.

Sample size

The sample size calculation was based on median time to healing. Lambourne *et al.*⁹ and Vowden *et al.*¹⁰ found that 60% of large ulcers (> 10 cm²) and 60% of ulcers of >6 months' duration (treated with four-layer compression) healed in 24 weeks. This represents a median time to heal of 15–22 weeks (estimated from published survival curve). Our sample was to include some smaller ulcers, but importantly it would also include people with *both* high ulcer duration *and* large area (of whom between 13% and 37% heal at 24 weeks with high compression),⁸ and therefore, overall we estimated that 50% of ulcers in the standard care group would heal within 22 weeks (compared with 11 weeks for small, new ulcers as determined in VenUS I).⁷

Estimating that clinicians and patients would value a reduction in healing time of 7 weeks (i.e. from 22 weeks to 15 weeks), we based our sample size calculation on this premise. This moderately sized effect was deemed as being required before clinicians would introduce a new therapy, with the consequent requirements to undergo training, arrange for purchase and servicing of machines, etc. To give us 90% power to detect this 7-week difference in median healing time we required a sample size of 306 patients, or 336 patients allowing for 10% attrition. This sample size also gave us 80% power to detect an 8-week reduction in median time to healing from 24 weeks and 90% power to detect an 8-week reduction from 26 weeks.

Approvals obtained

The York Multicentre Research Ethics Committee (MREC) approved the study on 4 February 2005. The details of the MREC, Local Research Ethics Committees (LREC) and Research and Development Department approvals are provided in *Appendix 2*. The trial was assigned the International Standard Randomised Controlled Trial Number (ISRCTN) of ISRCTN21175670; EudraCT number 2004-004911-51 and National Research Register number N0484162339.

Trial sites

The study was conducted in 11 UK sites and one Irish site (Dublin). These sites were recruited throughout the duration of the study and represented a range of urban and rural settings plus a number of different types of leg ulcer service. Details of the study sites are provided in *Appendix 3*.

Participant eligibility

Only people with 'hard-to-heal' venous leg ulcers were to be recruited into this study. For the purpose of this study a hard-to-heal venous leg ulcer was considered to be any break in the skin on the leg (below the knee), which either (a) had been present for >6 weeks or (b) occurred in a person with a history of venous leg ulceration. A participant was considered to have a venous leg ulcer where there was no other evident causative aetiology, the ulcer appeared clinically venous (moist, shallow, irregular shape, venous eczema, ankle oedema, and/or lipodermatosclerosis, not confined to the foot), and the study participant had an Ankle–Brachial Pressure Index (ABPI) of ≥ 0.8 . An ABPI of < 0.8 indicates that there is a high probability that arterial insufficiency is present and that the ulcer should not be regarded as venous.³³

Prognostic studies have found that patients with ulcers larger than 5 cm² and with duration of >6 months are less likely to heal within 24 weeks.³⁴

Inclusion criteria

All people with venous leg ulcers were potentially eligible for inclusion in the proposed trial if they met the following criteria:

1. They were receiving care from community/leg ulcer/outpatients nurses in trial centres.
2. They were able to give written informed consent to participate in the study. Information sheets and consent forms were to be provided in languages other than English if required.
3. The primary cause of their ulcer was chronic venous insufficiency. This diagnosis was made using the same diagnostic criteria currently employed by caregivers in the community, namely the clinical appearance of the ulcer, patient history and an ABPI to rule out arterial insufficiency.³³
4. They had 'hard-to-heal ulcers' as defined by the presence of at least one of these criteria:
 - i. a venous ulcer of >6 months' duration
 - ii. a venous ulcer >5 cm².
5. They had Doppler-determined ABPI of ≥ 0.8 measured within last 3 months.
6. Those with an ulcer infection (based on a clinical signs and symptoms checklist) at baseline were eligible to participate once the infection had been resolved.³⁵
7. Those who were unable to self-complete the English language QoL tools were still eligible to participate, but we did not collect QoL data from them [the Short Form questionnaire-12 items (SF-12) is validated in English, Spanish, Italian, French and German and we anticipated that the number of non-English speakers who use these languages would be very small, based on previous trial experience].

Exclusion criteria

Potential participants were excluded if they met the following criteria:

1. Their leg ulcer was due to causes other than venous insufficiency (e.g. arterial insufficiency, malignancy, pyoderma gangrenosum, etc.).

2. They had poorly controlled diabetes, as evidenced by a glycated haemoglobin (HbA_{1c}) of > 10%.
3. They had ankle prostheses/metal anywhere in the foot (e.g. pin and plate): because bone cement used in the replacement of joints has a high absorption capacity, the application of ultrasound to the ankle area may lead to heat damage of the prosthetic joint.²³
4. They had suspected thrombophlebitis: because the mechanical vibrations may cause an embolism.²³
5. They had active cellulitis: because of the potential risk of accelerated growth and dissemination of bacteria throughout the body.²³
6. They had suspected or confirmed local cancer/metastatic disease.²³

Patients previously enrolled into the study who had become ulcer free were not eligible for rerandomisation into the trial if their ulcer(s) recurred.

Recruitment into the trial

Local nursing staff, community nurses, leg ulcer nurses and trial nurses identified potential participants and supplied them with an information sheet about the trial (see *Appendix 4*). Patients were given a minimum of 24 hours to read the information sheet and consider participation. All potential venous leg ulcer patients were screened using a pre-trial screening form (see *Appendix 5*) which listed the main eligibility criteria. Patients potentially eligible and interested in participating were seen by their local trial nurse, who would discuss the study if more detail was requested, obtain written informed consent, record baseline data and administer the first allocated treatment. Participants' general practitioners (GPs) were notified of their involvement in VenUS III after recruitment. Information provided on the pre-trial screening forms was collected centrally at York Trials Unit to allow reasons for non-eligibility to be collated.

Baseline assessment

After written informed consent had been obtained, baseline data were collected on the patient using a Patient Record Form (see *Appendix 5*). The following data were collected.

Ulcer history and initial assessment

If the patient had more than one ulcer, nurses were asked to define which ulcer was the 'reference ulcer' (and therefore the reference leg), which was classed as the largest eligible ulcer. The outline of the reference ulcer was traced onto an acetate film grid marked with 1 cm² squares and an assessment was then made by the recruiting nurse of whether the reference ulcer area was ≤ 5 cm² or > 5 cm². The actual area was calculated at the York Trials Unit at a later date using the MOUSEYES computer program, Version 3.1 (Dr Robert John Taylor, Salford).³⁶ The reference ulcer was labelled according to leg (R for right; L for left) and the number 1 given to it (e.g. reference ulcer present on right leg = R1). Nurses completed tracings of all ulcers a patient had and labelled them in descending order of area (R2, R3, etc.) to allow follow-up of all ulcers on the limb.

Measurement of ankle-brachial pressure index

The result of a Doppler-determined ABPI measurement for the reference leg was noted along with the date it was measured. For inclusion in the study, this reading must have been obtained in the last 3 months as readings change over time.³⁷

Number of ulcer episodes on leg with reference ulcer

Data from VenUS I⁷ suggested that a greater number of ulcer episodes are prognostic of a longer healing time; we therefore recorded the number of ulcer episodes on the leg of the reference ulcer since the first episode.

Duration of reference ulcer and duration of oldest ulcer

Duration of reference ulcer was recorded based on participant report along with the duration of the oldest ulcer on the reference leg.

Patient mobility

Reduction in mobility can potentially contribute to ulceration by means of reduced venous return, secondary to calf muscle wastage.³⁸ It was recorded whether the patient was able to move freely, with difficulty or was immobile.

Ankle mobility, patient's height and weight

The VenUS I⁷ reported that, as well as ulcer area, duration and number of episodes, ankle mobility (full, reduced range or fixed), and body weight were also prognostic for healing. These data were all collected at baseline.

Ulcer position and image

For monitoring purposes a record of the position of all ulcers on the trial leg including the reference ulcer was made. A dated digital photograph was also taken of the reference ulcer.

Pain

Patients were asked to indicate how intense the pain had been in their reference ulcer during the past 24 hours using a visual analogue scale (VAS) ranging from 'no pain' to 'worst pain imaginable'. The minimum value on the scale was 0 mm and the maximum was 150 mm.

Date of birth

Date of birth was recorded at recruitment, allowing age at recruitment to be calculated. Increased age was associated with slower healing rates in one study.³⁸

Gender

The gender of participants was recorded, allowing a comparison with the existing information on the population of people with venous ulcers, in which women outnumber men.³⁹

Compression level

Whether the participant was currently being treated with two-, three- or four-layer high-compression bandaging was recorded.

Health-related quality of life

Participants were given a Baseline Questionnaire to complete prior to randomisation comprising the SF-12⁴⁰ and the European Quality of Life-5 Dimensions (EQ-5D).⁴¹

Randomisation

Participants were randomised equally between the two trial arms: ultrasound plus standard care and standard care alone. Randomisation was carried out using varying block sizes of four and six participants. To maintain allocation concealment the generation of the randomisation sequence and subsequent treatment allocation were performed by an independent, secure, remote, telephone randomisation service (York Trials Unit). The computerised randomisation system

was checked periodically during the trial following standard operating procedures. Owing to the nature of the intervention, it was not possible to conceal the treatment allocation from either the patient or the nurse.

Trial interventions

Participants were randomised to receive either:

- Low-dose (0.5 W/cm^2) ultrasound, 1 MHz, with a pulsed pattern of 1 : 4 as per trials by Callam *et al.*²⁹ and Lundeborg *et al.*²⁵ The ultrasound was to be applied to periulcer skin, weekly for up to 12 weeks, at regular dressing changes, plus standard care (see below for the definition of standard care). After the 12 weeks of ultrasound, patients returned to standard care alone.

or:

- Standard care: this was defined as a simple low-adherent dressing and high-compression, four-layer bandaging, reduced compression or no compression, according to the clinical assessment of the level of pressure tolerated by the patient. This is based upon UK Clinical Practice Guidelines.³³

Preparation for ultrasound treatment

Prior to the application of the ultrasound the leg would be washed and any loose skin from around the ulcer and remnants of emollients removed. The ultrasound was applied directly to the skin surrounding the ulcer, using a water-based contact gel to ensure passage of the waveform from the transducer to the tissues.

Target ulcer

The ultrasound treatment was applied for 5–10 minutes to the previously defined reference ulcer (see *Appendix 6*).

Calculating ultrasound treatment time

Previous studies had applied ultrasound for varying amounts of time. We sought to balance the need for larger ulcers to have more treatment time, the need for treatment time to be feasible as an addition to standard practice, and the need for a simple system to help nurses titrate ultrasound to the various patients she or he would see.

Ulcers of area $< 5 \text{ cm}^2$ received 5 minutes' ultrasound; those of 10 cm^2 or larger received 10 minutes' ultrasound. For ulcer areas between 5 and 10 cm^2 , the treatment time in minutes was calculated as the ulcer area in square centimetres (for example: an ulcer calculated as 6 cm^2 received 6 minutes of ultrasound). Ulcer area was recalculated every 4 weeks using acetate film grids with pre-printed 1 cm^2 areas.

Concurrent therapy

All dressings and bandages were to be replaced at each visit, as per standard practice. Concurrent therapy for all patients was low-adherent dressings and four-layer high-compression bandaging, reduced compression or no compression, according to the clinical assessment of the level of pressure tolerated by the patient. Should a change from the low-adherent dressing or the prescribed level of compression be required, in the opinion of the clinician, then this was recorded. The patient did not withdraw from the trial should the concurrent therapy change.

Nurse training

Prior to the trial starting, participating nurses attended a training programme on the rationale for the trial, patient eligibility, recruitment procedures (including consent and randomisation), ultrasound treatment application, data collection (completion of trial documentation and tracing ulcer outlines), handling participant withdrawal and adverse event reporting (see *Appendix 7*). Competency in ultrasound administration was assessed at the end of the training. The trained trial nurses were also permitted to cascade training in delivering ultrasound for the purposes of the trial to other local nurses so that treatments could be maintained during holiday periods or staff absences.

Checks were made by the local trial nurses regarding the use of ultrasound within the trial, to ensure that the ultrasound was being delivered as per protocol.

Ultrasound machines

The ultrasound machines were supplied, at discounted price, by EMS Physio Ltd, the largest UK manufacturer of ultrasound machines. The machine chosen was the EMS Therasonic 355 Physiotherapy system (EMS Physio Ltd, Wantage) which delivers only 1 MHz ultrasound: effective radiation area 4 cm², with a large transducer head, collimated beam, and beam non-uniformity ratio (BNR) < 5. We used a pulsed mode; each pulse lasted 2 milliseconds and the pulse ratio was 1 : 4. Prior to acceptance, all machines were tested at the National Physical Laboratory (NPL) to confirm that they were delivering ultrasound at the necessary frequency and intensity.

Auditing ultrasound machine performance

The ultrasound machines were assessed after 3 months' recruitment and 3-monthly thereafter to check the intensity of ultrasound delivered. Checks were undertaken by the ultrasound machine suppliers. These originally took place at each clinical site by the ultrasound machine suppliers except where there were no available engineers (Northern Ireland and Scotland). Previous studies have indicated that there are differences between the 'nominal' dose and that actually delivered by the machines.⁴² Some of this is apparent at machine delivery, and some is due to drift or step changes in output.⁴³ Each ultrasound machine was numbered so that patients who received treatment from individual machines could be identified. This check took place when a site had been recruiting for 3 months and 3-monthly thereafter.

Ultrasound therapy arm

During the 12 weeks of ultrasound therapy, the date of every nurse visit was recorded in an Ultrasound Treatment Log Booklet by the treating nurse, along with location and whether or not ultrasound had been applied and, if so, for how long, machine number and signature of the nurse applying it for (see *Appendix 5*). Information relating to dressings and bandaging applied was also recorded. Reasons for any changes in these from the previous visit were requested. If for any reason the patient was not given his or her weekly ultrasound treatment (infection, illness, non-attendance, etc.), that week was not carried over. Thus, the maximum number of ultrasound treatments a patient could receive was 13 (one at baseline plus one per week for a total of 12 weeks).

After the patient's ultrasound treatment period had finished, treatment reverted to standard care alone with the visit dates, locations, dressings and bandage changes recorded in a separate booklet – Dressing Log Booklet (see *Appendix 5*). Follow-up then continued as per the protocol.

Standard care arm

Visits to patients allocated to standard care alone with the visit dates, locations, dressings and bandage changes were recorded in the Dressing Log Booklet (see *Appendix 5*). Follow-up continued throughout their treatment period as per the protocol.

For all patients, acetate film tracings of all ulcers and digital photographs of the reference ulcer were taken every 4 weeks until 12 months after randomisation (or between 6 and 12 months in some cases depending on when they were recruited in the trial recruitment period) or the patient became ulcer free, whichever happened first.

Participant follow-up

Appendix 8 shows a summary of VenUS III.

Trial completion

Participants were deemed to have exited the trial when:

- The participant became ulcer free.
- The participant had been in the trial for 12 months (or between 6 and 12 months in some cases depending on when they were recruited in the trial recruitment period).
- The participant wished to exit the trial fully.
- The participant's doctor or nurse withdrew him or her from the trial.
- The participant was lost to follow-up.
- The participant died.

Participants whose reference ulcer had healed but who still had a venous ulcer (because the reference ulcer was not their only ulcer) continued to have routine clinical data collected about them until they became ulcer free or they had been in the trial for > 12 months (or between 6 and 12 months for cases recruited during the last months).

Instead of withdrawing fully from the trial, participants had the option of:

- withdrawing only from nurse data collection by the nurse
- withdrawing only from receiving the trial treatment
- withdrawing only from postal questionnaires; or
- any combination of the above.

Patients who elected to withdraw from all three (data collection, trial treatment and postal questionnaires) were deemed to be full withdrawals (trial exit). Nurses were able to indicate any change in the patient's level of participation by completing a Change of Circumstances Form (see *Appendix 5*). This ensured appropriate follow-up from the Trials Unit.

Measurement and verification of primary measure

The primary end point was time to healing of the reference ulcer.

Secondary outcomes were cost-effectiveness of ultrasound, proportion of patients with ulcers healed at 3, 6 and 12 months, percentage and absolute change in ulcer size, HRQoL and adverse events.

Determination of reference ulcer healing

Healing was defined as 'full epithelial cover without a scab, where a scab is a thick crust over the wound'. This meant that an ulcer in which there was full epithelialisation overlaid by a thin

layer of dry skin could be classified as healed. Clinically, this type of wound would not require a primary contact layer.

When the treating nurse deemed the reference ulcer to be healed, she or he completed an Ulcer Healed Form (see *Appendix 5*) and took a digital photograph of the healed ulcer (see *Appendix 9*). In addition, nurses were asked to take another digital photograph 7 days after they had considered the reference ulcer healed.

Two blinded assessors independently assessed all photographs for each participant to determine a date for healing. This assessment followed the same successful process as that used in VenUS II.⁴⁴ The assessors discussed any discrepancies with referral to a third assessor for a final decision if required. The primary outcome was calculated using the date of healing as decided by the blind assessors. However, if no photographs were available for a participant, then the date of healing decided by the treating nurse was taken as the healed date.

Measurement and verification of secondary outcomes

Collection of resource use data

During their treatment period within the study, data were recorded (see *Appendix 5*) about treatment received, location of the visit and the level of compression bandaging applied.

At recruitment and 3, 6, 9 and 12 months after randomisation, patients were asked to complete a questionnaire on health and social care resource use during the previous month (see *Appendix 5*). The questionnaire was designed for participant completion and was returned to the trial office using a reply-paid envelope. Participants indicated how many times in the previous month they had used health services (e.g. seen a GP or nurse or received hospital care) and whether any health service use was ulcer related. The collection of self-reported resource use data was continued until the patient had been in the study for 12 months (or between 6 and 12 months for cases recruited during the last months).

Proportion of ulcers healed at 3, 6 and 12 months

The proportion of reference ulcers healed at 3 and 6 months post randomisation was reported to summarise the effects of the two regimens. Proportions healed are commonly used in wound care trials and hence this allowed us to compare our results directly with other trials which have rarely used time to event data.

Proportions of time patients are ulcer free

Reduction in recurrence would help reduce the prevalence of this condition and thus costs. Crude recurrence rates are potentially biased by any difference in healing rates associated with the two groups (ultrasound or standard care). As the treatment group which experiences faster healing is, by definition, exposed to more risk of recurrence if one group has more rapid healing, then people in that group are at risk of earlier recurrence. To account for this we used the proportion of time that patients were ulcer free. Patients with healed ulcers were contacted by telephone at 6, 9 and 12 months (up to June 2009) after healing in order to obtain recurrence data.

Percentage and absolute change in ulcer size

Data collected at 1, 3 and 12 months post randomisation allowed us to determine the reduction in ulcer area in patients who did not achieve complete ulcer healing. If the ultrasound and standard care groups achieved similar times to complete healing but one resulted in larger changes in ulcer area, then this may be clinically important as smaller ulcers may exude less

and therefore require less frequent dressing changes. Furthermore, the recording of ulcer area at these time points allowed further study of the trajectory of healing for venous leg ulcers and the relationship between the reduction in ulcer area and eventual healing.

One study found that increased ulcer area at 1 month after initiation of treatment is a useful predictor for non-healing.⁴⁵ Identifying patients who are likely to fail to heal early in treatment allows these patients to have prompt referral to specialist centres for further assessment and treatment. Measurement of ulcer size involved taking tracing using acetate wound grids and a fine-nibbed, indelible pen, taking the outer edge of the ulcer rim as the outer edge of the tracing line (i.e. ulcer area = area enclosed by tracing and area of line). Ulcer area, as determined by acetate tracing, is an accurate and reliable measure.⁴⁶

Health-related quality of life

Participants were asked to answer questions relating to their HRQoL throughout the study, when they were asked to complete two generic instruments (EQ-5D and SF-12). Generic instruments were used to measure participants' perceptions of health outcome in this trial, which have previously been shown to be sensitive to changes venous ulcer healing status.⁴⁷ In addition, these instruments are also particularly useful for comparing groups of participants, while also having a broad capacity for use in economic evaluation. Their generic nature also makes them potentially responsive to side effects or unforeseen effects of treatment.

Each participant's perception of his or her general health was assessed using the acute version of the SF-12⁴⁸ and the EQ-5D (EuroQol).⁴¹ The SF-12 is a reliable and well-validated questionnaire,⁴⁹ and has been used in UK populations including older people and leg ulcer patients.^{50,51} We used a layout of the SF-12 shown in previous work to yield improved response rates and quality.⁵² The EQ-5D is a generic measure of health status, in which health is characterised on five dimensions (mobility, self-care, ability to undertake usual activities, pain, anxiety/depression).⁴¹ Participants were asked to describe their level of health on each dimension using one of three levels: no problems, moderate problems and severe problems. Each response locates a person into one of 243 mutually exclusive health states, each of which has previously been valued on the 0 (equivalent to dead) to 1 (equivalent to perfect health) 'utility' scale based on interviews with a sample of 3395 members of the UK public.⁵³ The EQ-5D has been validated in the UK and questionnaires containing both instruments were administered to patients by postal survey at baseline and at 3, 6, 9 and 12 months.

Optimising questionnaire response rates is of vital importance, and a recent systematic review has investigated strategies to increase questionnaire response rates.⁵⁴ The review reported that response rates to postal questionnaires doubled (odds ratio = 2.02, 95% CI 1.79 to 2.27) when a financial reward was included with the questionnaire compared with rates obtained with no incentive. The response rate increased further when the incentive was not conditional on response versus upon return of questionnaire (odds ratio = 1.71, 95% CI 1.29 to 2.26). Based on these data, we enclosed an unconditional payment to participants along with their final (usually the 12th month) questionnaire. They received notification in advance that would receive £5 in recognition of their commitment to our study and the time they spent completing questionnaires.

Adverse events

An adverse event is defined as 'any undesirable clinical occurrence in a subject, whether it is considered to be device related or not'.⁵⁵ Both treatment-related and -unrelated adverse events were reported to the trial office (see *Appendix 5*). The reporting nurse indicated whether, in his or her opinion, the event was related to trial treatment or not. Events were also classed as serious or non-serious. Serious adverse events (SAEs) were defined as death, life-threatening risk, hospitalisation, persistent or significant disability/incapacity and patient being newly diagnosed

as diabetic. For other events the treating nurse made a clinical decision about the seriousness. A list of possible treatment-related adverse events was established a priori, based on reports in the literature and VenUS I and VenUS II. These were pressure damage, infection, skin damage surrounding ulcer, new ulcer, ulcer deterioration and also adverse reaction to the ultrasound treatment or gel.

All nurses were asked to report any SAEs within 24 hours of the event occurring, or within 24 hours of becoming aware of the event. Sites were also provided with review forms in order to follow up all events so that information on eventual outcomes was recorded.

Clinical analysis

The objective of the clinical analyses was to compare the clinical effectiveness of low-dose ultrasound (0.5 W/cm² spatial average and temporal peak) delivered at 1 MHz plus standard care with standard care alone in the treatment of hard-to-heal venous ulcers (i.e. those with duration of > 6 months and/or surface area > 5 cm²). Our aim was to assess whether the addition of 5–10 minutes of ultrasound (depending on ulcer area) to a package of best available standard care had any affect on:

- time to ulcer healing
- complete ulcer healing (the patient is completely healed of all ulcers)
- HRQoL
- adverse events.

Outcomes

Primary

- Time to complete healing of the reference ulcer.

The reference ulcer was the largest ulcer on either leg (as assessed at the time of trial entry). The date of healing was recorded by the research nurses on the Ulcer Healed Form and the photographs of the reference ulcer as assessed independently by two people blind to treatment group. Any disagreements were resolved by discussion or referral to a third blinded assessor. The primary outcome was calculated using the date of healing as decided by the blind assessors. If the blinded assessors did not agree on a healing date, then the date as recorded on the Ulcer Healed Form was used. Time to healing was derived as the number of days between randomisation and the first date that healing was confirmed. Patients who withdrew unhealed from the trial or died prior to healing were treated as censored in the analysis. Their time to censoring was derived using the date of trial exit, the date of their last ulcer assessment or the date of trial closure. Patients who completed the full 12-month follow-up without their reference ulcer healing were also treated as censored and their time to censoring was calculated as 12 months (365 days).

Secondary

- Reduction in ulcer area.
- HRQoL (SF-12) (baseline and 3, 6, 9 and 12 months).
- Complete healing of all ulcers during the trial period (up to 12 months).
- Adverse events.
- Ulcer recurrence.

Analyses

Primary statistical analyses were performed on an intention-to-treat basis using a two-sided, 5% significance level.

Primary outcome

The primary analysis compared the time to complete healing of the reference ulcer between the two randomised groups using a Cox regression model.⁵⁶ The analysis adjusted for centre as a random effect, ulcer area (from baseline tracing), ulcer duration and whether or not the patient was treated with high-compression bandaging. If centres recruited a small number of patients (five or fewer) then the analysis was repeated with no adjustment for centre, as a sensitivity analysis. Hazard ratios and corresponding 95% CIs were presented. The assumption of proportional hazards was checked using log–log plots, inclusion of interaction terms in the model (for each term with time) and by looking at plots of Schoenfeld residuals. The linearity assumption of continuous terms in the model (ulcer area and duration) was assessed using plots of the Martingale residuals and, if necessary, a suitable transformation used.

Kaplan–Meier survival curves were produced for the two groups and the median time to healing with 95% CI, as well as the Kaplan–Meier estimates of the proportions of ulcers healed at 12 and 24 weeks (for comparison with the results of other venous leg ulcer trials) presented.

A sensitivity analysis was performed to repeat the primary analysis using only the data of healing as recorded by the research nurses, and not using the data from the photographs.

Agreement on date of healing

The Cohen's kappa measure of inter-rater agreement was used to assess agreement between the two assessors of the photographs for time to healing. This was repeated to look at agreement between the final decision from the photograph assessment and the nurses' recorded date of healing.

Secondary outcomes

Ulcer area

Ulcer area tracing data were measured using a specialist computer package (MOUSEYES).³⁶ The areas at baseline and each assessment were summarised using descriptive statistics [mean, standard deviation (SD), median, range]. Previous research has shown that the initial reduction in ulcer area (percentage reduction after 4 weeks of good wound care) is predictive of eventual healing.⁴⁵ Therefore, we compared the initial healing rates between the ultrasound and standard care groups. The ulcer area at week 4 was compared between treatment groups using analysis of covariance to adjust for baseline ulcer area, centre, ulcer duration and use of compression.

Quality of life

Quality of life was measured using the SF-12 questionnaire [measured at baseline (0), and at 3, 6, 9 and 12 months]. The scores for the physical and mental health components were analysed using a multilevel regression model approach. The outcomes at each time point were used in a single model, with time points nested within patients to account for within-patient correlation in scores. The model was used to estimate the difference between treatments over the whole 12-month follow-up period. The outcome modelled was the score at each follow-up assessment and the covariates included in the model were centre, baseline health component score, baseline ulcer area, ulcer duration, use of compression and time (indicators for 0, 3, 6, 9 and 12 months). Whether the pattern in QoL scores over time is different between the two treatments was assessed by including an interaction term between treatment and time in the model.

The assumption of normally distributed data was assessed and, if necessary, log transformations or other analysis methods used.

The numbers of patients with missing data at each time point were summarised together with reasons for missing data (if available). We summarised the proportions of missing questionnaires

at each time point by healing status and used joint modelling of repeated QoL data and time to ulcer healing.⁵⁷

Complete healing of all ulcers at 12 months

The proportions of patients completely healed of all ulcers on both legs by the end of trial follow-up (12 months or earlier) were summarised by treatment group. A Kaplan–Meier plot of the time to complete healing and estimates of the median time to complete healing and 95% CI for each group was presented. Any patient not completely healed by the end of the trial was treated as censored.

Ulcer recurrence

The proportions of patients whose reference ulcer healed and then recurred was summarised by treatment group.

Adverse events

The number of adverse events experienced by each patient was compared between treatment groups using a negative binomial model adjusting for the same covariates as the primary analyses (centre, ulcer size, ulcer duration, use of compression). This analysis summarised all adverse events and then SAEs and non-serious adverse events (NSAEs) separately. The number of patients with one or more adverse events and the numbers of adverse events, their severity and whether they were considered treatment related or not, were summarised descriptively by treatment group.

Economic analysis

Economic evaluation of health interventions is a tool used to assist decision makers in prioritising and allocating resources in the health-care sector, by assessing the value for money (cost-effectiveness) of alternative interventions.⁵⁸

The aim of the economic evaluation was to assess cost-effectiveness of low-dose ultrasound in conjunction with standard care compared with standard care alone in the treatment of hard-to-heal venous leg ulcers. Using individual-level data, cost-effectiveness analysis and cost-utility analysis were performed. These analyses are expected to provide evidence, taking into account both comparative cost and effectiveness simultaneously, to assist the decision on whether or not to adopt ultrasound in conjunction with standard care for the treatment of hard-to-heal venous leg ulcers.

The analysis was conducted on an ‘intention-to-treat’ basis, comparing incremental costs with incremental ulcer-free days (cost-effectiveness analysis) and incremental quality-adjusted life-years (QALYs) (cost-utility analysis). The perspective of NHS and Personal Social Services was adopted in the current analysis considering that the findings will be used to inform the decision maker in the NHS. Discounting for the future cost and health outcome was not necessary as the time frame of the trial was 12 months after randomisation. The year of pricing was 2007. The analyses were conducted using STATA 10 (StataCorp, College Station, TX, USA).⁵⁹

Data

Cost and health benefits data used in the economic analysis were extracted from the current trial. There were two sources of cost data: nurse-completed and patient-completed questionnaires. Nurse-completed questionnaires provide detailed information on each treatment the patients received, such as the choice of compression therapy, the duration of ultrasound treatment (if

applied) and the treatment setting, whereas patient-completed data, derived from patient self-reported questionnaires at 3-, 6-, 9- and 12-month follow-up, provided information on frequency of health-care consultations, including doctor, nurse and hospital outpatient visits. Two different measures of health benefit were used: the time to healing and QALY. Time to healing was recorded by nurses and assessed by blinded investigators, whereas QALYs, representing years living in full health, were calculated based on information obtained from patient self-reported questionnaires every 3 months. Details of each constituent component of the economic analysis are discussed in the following sections.

Owing to the restricted follow-up period (1 year) as well as death and loss to follow-up, censoring occurred in both cost and health benefits data. To adjust for this censoring issue, in order to obtain more accurate estimation, the inverse probability weight (IPW) approach⁶⁰ was applied. This method applies a set of different weights to account for the censoring. The same approach was used in VenUS II.⁶¹ Taking the time to healing as an example, in this IPW approach only participants with observed time to healing data contribute with non-zero terms, but their contributions are inversely weighted by the probability of being observed.⁶¹ Consequently, individuals who are less likely to be observed are weighted most heavily. The censoring distribution was estimated through the Kaplan–Meier estimator. Similarly, an IPW approach was adopted in the estimation of mean costs and QALYs to adjust for the censoring issues in the cost and QALY data, respectively.

Outcomes of the economic analysis

The economic analysis used incremental costs and incremental health benefits, estimated from the trial data, to evaluate the value for money of the ultrasound with standard care treatment. Time to healing of the reference ulcer and QALYs were the units of health benefit in the cost-effectiveness analysis and cost–utility analysis, respectively.

Health benefits

Time to healing estimation

The mean time to healing was estimated from the IPW regression using the same covariates as in the clinical analysis to adjust for the nature of the censoring, possible baseline imbalances and randomisation stratification, namely baseline ulcer duration (logarithmic), ulcer area (logarithmic), use or not of compression therapy and centres (aggregating centres with fewer than five cases). The centre effect was treated as fixed effect in all subsequent analyses. In order to facilitate the interpretation of the cost-effectiveness analysis, the effectiveness outcome was reported as ‘gain in ulcer-free days’. The gain in ulcer-free days is the same as the difference in mean time to healing between two trial arms (same absolute value), but with the opposite sign (−/+).

Utility scores and quality-adjusted life-year estimation

Utilities of patients were measured by the EQ-5D⁶² questionnaire at baseline and at each follow-up of 3, 6, 9 and 12 months, independent of healing status. EQ-5D is one of the most widely used HRQoL measures and provides summary index (utility) scores of health states for the purpose of economic evaluation. The EQ-5D description system contains five dimensions – mobility, self-care, usual activities, pain/discomfort and anxiety/depression; each dimension has three levels – no, some and severe problems. The utility, also known as EQ-5D index score, of each patient at each observed time point was derived from patient’s responses to the EQ-5D description system at that time point and a predefined weight was assigned accordingly. The predefined weight represents the social preference of the general population in England and Wales towards EQ-5D health states.⁶³ These utility scores, 1 representing full health and 0 indicating death, were then used in QALY calculation.

According to the data collection, the study time horizon was partitioned in homogeneous subintervals (quarterly intervals). Quarterly QALYs were calculated by multiplying an individual's utility score with survival time using the area under the curve approach, which was defined by linearly interpolating the utility scores measured over time.⁶⁴ However, not all participants were followed up for a full trial period because of censoring. To account for the impact of censoring, thus avoiding biased estimates, mean quarterly QALYs were estimated using the IPW method. To ensure comparability with the clinical analysis, linear regression was used to adjust QALYs by the same clinical covariates and also baseline utility. In the presence of imbalance, failure to include baseline utility results in biased results and a misrepresentation of uncertainty.⁶⁵ QALYs were weighted by the inverse of the probability of an individual not being censored. In the case of participants who died, utility values were recoded as zero. Mean total QALYs, over the 12-month follow-up period were then estimated as the sum of the estimated mean QALYs per period for each trial arm given the mean value of the rest of the covariates observed in the whole sample.

Resource use and unit costs

A cost for each trial participant was calculated as the product of resources used and their relevant costs. The analysis was costed at 2007 prices (mid-point of the trial). Three components were considered in the estimation of leg ulcer treatment cost: cost of ultrasound machine, cost of compression therapy and cost of health-care consultations (focusing on cost of health-care provider's time). Other treatments, such as primary and secondary dressing or skin preparations, were assumed to be used equally across treatment arms; these resources were not included in the economic analyses. Incorporating costs categorised as irrelevant in distinguishing treatments into the analysis will increase the variance (and the standard error) of total costs for each arm and, thus, misrepresent uncertainty in the incremental costs.⁶⁶

Cost of ultrasound machine

We purchased 40 ultrasound machines at a cost of £26,267.87 including the purchasing and testing fees as listed in *Table 2*. These fees are regarded as one-off equipment costs. Following the suggested method⁵⁸ for dealing with one-off equipment costs in economic evaluation, the study calculated the equivalent annual equipment cost, taking into account depreciation of the ultrasound machine and its opportunity cost. By assuming that the average lifespan of an ultrasound machine is 7 years and considering linear depreciation with the interest rate for opportunity cost at 3.5%, the equivalent annual equipment cost over the period of 7 years is £4659.15. The information on lifespan and cost of ultrasound machines was provided by the machine supplier (EMS Physio Ltd). The interest rate chosen here was based on the discounting rate suggested in the reference case for technology appraisal recommend by National Institute for Health and Clinical Excellence (NICE).⁶⁷ Note that discounting was not applied in the current analysis.

The cost of ultrasound machines per patient in the treatment arm was estimated to be £88.05. This was calculated by summing the equivalent annual equipment cost of ultrasound machines

TABLE 2 Costs of ultrasound machine

Item	Total cost (£)	Note	Source
Machine purchasing fee	19,180.00	Forty machines	EMS Physio Ltd
Testing fee	7087.87	One-off at machine set-up	NPL
Equivalent annual equipment cost	4659.15	Assuming 7-year lifespan and an interest rate of 3.5%	
Servicing fee	10,133.71	Once every 3 months	EMS Physio Ltd
Cost of ultrasound machine per patient	88.05	Dividing the sum of the servicing fee and equivalent annual equipment cost by the number of participants in the ultrasound arm	

with their servicing fee through a year (occurring every 3 months), then dividing by the number of participants in the treatment arm. This cost was added to each participant in the treatment arm to calculate their total costs of leg ulcer treatment.

As detailed, the costs associated with the ultrasound machine were based on the cost of the current trial, and might not reflect the 'real' cost in other, more generalised, settings. For instance, if the ultrasound machines are also used for other purposes (therefore more patients use them), the cost of ultrasound machine per patient could be lower (as a result of a larger denominator). The impact of this estimation was explored in the sensitivity analysis.

Cost of compression therapy

Table 3 shows the unit cost of each compression bandaging system. The composition of the compression bandaging system was obtained from VenUS II and updated based on the supply and prices as listed in the *British National Formulary* (BNF).⁶⁸ The choice of the class of compression therapies was recorded by a nurse at each treatment (*high compression*: four-layer, three-layer, two-layer and short-stretch high compression; *low compression*: three-layer reduced compression; light compression). As no information on the size or brand of the system was available, an arithmetic average cost for commercially available systems was used to cost the class recorded. The cost of compression therapy per patient/per visit was then calculated accordingly.

Cost of health-care consultation

Both nurse- and patient-reported data regarding visits to or from health-care providers were available. Unless patients refused, nurse-reported data were intended to record every single nurse-administered ulcer treatment a participant received until healed, death or end of follow-up. Therefore, nurse-reported data comprised ulcer-related resource use only. Health-care consultations in patient self-reported data were extracted from the follow-up questionnaires (every 3 months). Participants were asked how many times they had seen a doctor or nurse and had been to hospital as an outpatient in the past 4 weeks and how many consultations were related to their ulcer. There were a large number of missing data regarding health-care consultations (for instance, the missing rates for patient-reported nurse visits are 28%, 32%, 37% and 38% in the 3, 6, 9 and 12-month follow-up questionnaires, respectively) so we used the nurse-reported data for the base case, while the use of patient-reported data were explored in a sensitivity analysis.

The cost per nurse visit was calculated by multiplying the duration of each visit by the cost per minute of nurse consultations, which varied depending on the location of treatment (Table 4). There was, however, no direct information available in the current trial for the duration of each nurse visit. We followed the approach used in VenUS I,⁷ in which the duration of a home visit was assigned as 40 minutes and a clinic visit as 22 minutes. The number was taken from the national estimates and was in agreement with a survey conducted within VenUS I to investigate the duration of time nurses spent on treating ulcer patients. Therefore, in the current study it is assumed that the duration of a nurse home visit was 40 minutes and all other visits were 22 minutes. When the visits included ultrasound treatment, the amount of time to apply ultrasound, as recorded by nurses, was added to the duration of visits.

All cost units/values regarding nurse consultation are listed in Table 4. The sources of costing include the VenUS I trial and the costs of health and social care published by the Personal Social Services Research Unit (PSSRU), University of Kent.⁶⁹

In the current trial, adverse events were recorded by the nurse. However, there was too little information available to allow for an accurate estimation of costs associated with these episodes. Therefore, the cost of adverse events was ignored in the base-case analysis. In sensitivity analysis,

TABLE 3 Unit cost of compression bandaging system

Bandaging system	Example	Cost (£) (from BNF)	
High-compression bandaging: 4LB	K-Four®	6.25	
	Profore®	8.35	
	System 4®	7.77	
	Ultra Four®	5.67	
	<i>Mean cost</i>	<i>7.01</i>	
High-compression bandaging: SSB	Actiban®	3.18	
	Actico®	3.21	
	Comprilan®	3.12	
	Rosidal K®	3.36	
	Silkolan®	3.39	
	<i>Mean cost</i>	<i>3.25</i>	
High compression: two-layer kits	ProGuide®	8.49	
	Coban®	8.08	
	<i>Mean cost</i>	<i>8.29</i>	
Layer 1	Advasoft®	0.39	
	Cellona Undercast padding®	0.42	
	Flexi-Ban®	0.44	
	K-Soft®	0.4	
	Ortho-Band Plus®	0.37	
	Softexe®	0.58	
	Ultra Soft®	0.42	
	Velband®	0.66	
	Surerpress®	0.53	
	Profore #1®	0.62	
	<i>Mean cost</i>	<i>0.48</i>	
	Class 2	Neosport®	0.99
		Soffcrepe®	1.14
Setocrepe®		1.18	
Profore #2®		1.16	
K-Lite®		0.89	
<i>Mean cost</i>		<i>1.07</i>	
Class 3A	Elset®	3.06	
	Elset S®	5.13	
	K-Plus®	2.17	
	Profore #3®	3.46	
	<i>Mean cost</i>	<i>3.46</i>	
Cohesive	Coban®	3.61	
	Profore #4®	2.86	
	Hospifour # 4®	1.93	
	<i>Mean cost</i>	<i>2.80</i>	
Class 3C	Setopress®	3.46	
	Tensopress®	3.47	
	Profore Plus®	3.24	
	<i>Mean cost</i>	<i>3.39</i>	
Compression systems (using mean costs presented)	<i>Three-layer high compression: 1, 3C, cohesive</i>	<i>6.67</i>	
	<i>Three-layer reduced compression: 1, 2, cohesive</i>	<i>4.36</i>	
	<i>Light compression: 1, cohesive</i>	<i>3.28</i>	

4LB, four-layer bandaging; SSB, short-stretch bandaging.

TABLE 4 Unit costs and duration of nurse consultations

Item	Mean unit value (£ or minutes)	Source
<i>Nurse consultation (per minute)</i>		
Community	1.00	PSSRU
Home visit	1.07	PSSRU
Travel cost for home visit	1.40	PSSRU
GP surgery	0.48	PSSRU
Hospital	0.63	PSSRU
<i>Duration of nurse consultation</i>		
Home visit	40	VenUS I
Other visit	22	VenUS I

however, further resources used, e.g. hospital visits, were self-reported by patients. Thus, in this alternative analysis possible resource consumptions due to adverse event might be captured.

Total cost estimation

Resource use data are also subject to censoring, and estimating the mean total cost based on complete case analysis will underestimate the true expected costs. An IPW regression (as described above) was used to account for censoring, possible baseline imbalances and randomisation stratification variables. Mean cost estimation was made by partitioning the study period into quarterly periods and the IPW regression estimates obtained for each period were then summed to obtain the total expected costs.

Cost-effectiveness

To assess cost-effectiveness, the mean difference in costs between trial arms was compared with the mean difference in health benefits. For instance, if ultrasound plus standard care is more expensive and is associated with fewer health benefits than standard care alone, then ultrasound with standard care is dominated by standard care alone and the decision whether or not to adopt ultrasound is straightforward (not adopt). The decision arising from the converse situation (in which ultrasound plus standard care is dominant, i.e. less costly *and* more beneficial than standard care alone) is similarly straightforward (adopt). However, if ultrasound is more costly and more beneficial or less costly and less beneficial than standard care, we need to assess whether the increased cost of the ultrasound is worth the increased benefit, or whether the reduced benefit conferred by the ultrasound is justified by the reduced cost.

To ascertain the cost-effectiveness of a health-care intervention relative to another in the absence of dominance, an incremental analysis of cost-effectiveness is conducted. The incremental cost-effectiveness ratio (ICER) is the most commonly used cost-effectiveness measure and combines costs and health benefit in a single measure to which a decision rule for cost-effectiveness can be applied. It combines costs and benefits in a ratio of the mean difference in cost between the alternative treatments being compared with the mean difference in health benefits:

$$\text{ICER} = \frac{C_1 - C_0}{B_1 - B_0} \quad [\text{Equation 1}]$$

where C_1 and B_1 are, respectively, the mean costs and mean health benefits associated with the technology under evaluation (ultrasound with standard care in the current analysis), while C_0 and B_0 are the mean costs and mean health benefits associated with the comparator technology (standard care alone).

The decision rule for cost-effectiveness on the basis of the ICER indicates that a treatment strategy can be considered cost-effective only if the decision maker's willingness to pay for an additional unit of health benefit (QALYs and ulcer-free days) is greater (or equal) to the ICER. According to NICE, the willingness to pay for an additional QALY ranges between £20,000 and £30,000.⁶⁷ Therefore, if the results of a cost-utility analysis (the estimated cost per QALY) is below this threshold, the intervention will be considered cost-effective.

Cost-effectiveness analysis in which the outcome is expressed in a natural unit, for example cost per ulcer-free day, may be more intuitive for clinicians. Despite this, and for the purpose of informing adoption decisions, the results of cost-effectiveness analysis are harder to interpret because there is no information on the willingness to pay for an additional ulcer-free day. Without this information we cannot determine whether or not the new intervention is cost-effective. To inform a decision based on this measure of health benefit, a threshold has to be established, and the decision maker is responsible for establishing this. Another reason to include this type of analysis is to facilitate the comparisons between relevant studies.

Uncertainty assessment

There is uncertainty in the incremental cost-effectiveness between two interventions, and this can be summarised graphically in a cost-effectiveness plane. By plotting the non-parametric bootstrapping results – 4000 replicates of difference in costs and health benefits (QALYs and ulcer-free days), the position of the estimates can indicate the degree of certainty that one of the interventions is dominant (north-west or south-east quadrants).

The ICER is associated with uncertainty because its numerator (expected costs) and its denominator (effectiveness) are estimated with sampling uncertainty. Therefore, a decision on whether or not to adopt a treatment based on the ICER estimate is also associated with uncertainty. In other words, if the trial were repeated, we might observe a different mean incremental cost and effectiveness, resulting in a different ICER estimate. The analysis of the consequences of this uncertainty and the extent to which it impacts on the adoption decision should be investigated to inform whether further research is needed.⁷⁰ Thus, the uncertainty around incremental costs and effects estimates and its impact on the adoption decision were investigated here.

Confidence intervals

Uncertainty around the decision to adopt the treatment under evaluation was assessed through a non-parametric bootstrap resampling technique.⁷¹ This is a common methodology used to construct CIs around the incremental costs and health benefits from sampled cost and effectiveness random variables. Firstly, the bootstrap technique was used to sample (with replacement) from the observed cost and effectiveness pairs, maintaining the correlation structure. For each bootstrap resample, an IPW estimate of expected total costs, expected QALYs and expected time to healing was calculated, which allowed computation of cost-effectiveness and cost-utility outcome replicates. The 95% CIs for the differential costs and QALYs were then calculated using bias-corrected non-parametric bootstrapping.

Cost-effectiveness acceptability curves

To explore the decision uncertainty regarding the cost-effectiveness of ultrasound treatment, cost-effectiveness acceptability curves (CEACs) were plotted. The CEAC expresses the probability that an intervention is cost-effective in relation to the comparator intervention, as a function of the threshold willingness to pay.⁷² Thus, the CEAC summarises, for every value of willingness to pay, the evidence in favour of the intervention being cost-effective. In this case, given the trial data, the CEAC for ultrasound with standard care represents the probability of this treatment

being cost-effective compared with standard care alone for a range of willingness-to-pay values for an additional ulcer-free day/QALY.

Sensitivity analysis

Scenario 1

To explore the impact of the source of health-care consultation on cost-effectiveness/cost-utility analysis, a sensitivity analysis was conducted. In this analysis, patient-reported, instead of nurse-reported, data were used to calculate leg ulcer-related costs. Costs unrelated to leg ulcers were assumed to be equal between arms and were thus not considered in this analysis.⁶⁶ In contrast to the base-case analysis, in which only nurse consultations were costed, in this scenario we also considered ulcer-related hospital visits and doctor consultations. The cost per visit was calculated assuming different duration of home and clinic visits, as stated in *Table 4*. The self-reported data collected information about the visit setting (home or clinic). However, this information was recorded for all doctor/nurse/outpatient visits rather than for ulcer-related visits only. Consequently, we assumed that the setting of ulcer-related visits from self-reported data would follow the same pattern as that reported for all visits, for which data were available.

As shown in *Table 5*, the additional unit cost applied in this sensitivity analysis included doctor visit at GP surgery and at home, £31 and £50 per visit, respectively. Furthermore, the cost per hospital outpatient was charged as a non-consultant-led follow-up attendance fee, £71.

Scenario 2

One-way sensitivity analysis was also carried out to investigate the impact of the cost of the ultrasound machine on the total cost estimation. In the base-case analysis, the cost of the ultrasound machine was borne by the trial participants only (those in the treatment arm). In reality (such as the NHS setting), ultrasound machines are used for other purposes as well, e.g. tennis elbow and plantar fasciitis, therefore the cost of equipment per patient should be lower (shared by more users). This implied that in the current trial the average cost of the treatment arm was overestimated.

TABLE 5 Unit costs of other health consultations

Item	Mean unit value (£)	Source
<i>Doctor visit</i>		
GP surgery	31	PSSRU
Home visit	50	PSSRU
Hospital outpatient	71	PSSRU

Chapter 3

Protocol changes

Recruitment period

As stated in the original protocol, we planned to recruit 336 patients over an 18-month period with all participants being followed up for 12 months. As the study progressed, a low recruitment rate (despite the recruitment of extra study sites; *Appendix 3* details participation length of sites), led us to apply to the funder for an 18-month extension to the recruitment period (July 2007 to December 2008). The original sample size of 336 participants remained unchanged.

Follow-up

The extension to the recruitment period resulted in a variable duration of follow-up, depending on when the patient was randomised. The extension required that the last day of any follow-up was set as 30 June 2009 so that patients recruited between July 2008 and 31 December 2008 were followed up for periods ranging from 6 to 12 months. Patients were followed up, where possible, until they became ulcer free, in order to provide economic end points. In patients with only one ulcer, and in those in whom smaller ulcers healed before the reference ulcer healed, the date of healing of the reference ulcer was deemed to be the date of complete healing.

Inclusion and exclusion criteria

The study investigators felt that many people may have venous ulcers in the presence of rheumatoid arthritis and that an ulcer is not necessarily due to their rheumatoid disease. We had initially excluded this population as people with arterial inflammation may be more prone to compression damage, but given that the clinicians caring for these patients reported that they commonly used high compression, we decided to drop the exclusion criterion '*rheumatoid arthritis*'.

Similarly, clinical collaborators argued that people can have venous ulcers in the presence of diabetes mellitus, and that their ulcer may not be secondary to diabetes. We had initially excluded this population as, according to National Clinical Practice Guidelines, they would not be suitable for high compression. However, we were informed that in some clinical centres expert practitioners treated people with well-controlled diabetes and an expert vascular assessment, with high compression therapy. With well-controlled diabetes defined as a recent HbA_{1c} level of <10% we dropped the exclusion criterion '*diabetes*' and replaced it with the requirement that anyone with diabetes had an HbA_{1c} of <10%.

It was decided to drop the exclusion criterion of peripheral arterial disease, as it was felt to be unnecessary given that the inclusion criterion states that the ulcer must be primarily due to venous disease. If the recruiting nurse had considered someone for trial entry owing to the patient's clinical diagnosis of '*ulcer primarily due to venous insufficiency*' and the ABPI reading confirmed the lack of significant arterial insufficiency, it was felt appropriate to drop the exclusion criterion of '*peripheral arterial disease*'.

The original protocol for which we gained ethical approval was to recruit people with venous ulceration and an ABPI of at least 0.8 who are able to tolerate high-compression therapies. Again, our clinical collaborators argued that some people who are tolerant of only reduced compression therapy represent a particular challenge, as at present high-compression therapy is the single most effective element of treatment. It was then felt appropriate to drop the inclusion criterion of '*willing and able to wear four-layer high-compression bandaging*', as these patients (people with hard-to-heal venous ulcers unable to tolerate high compression) could be a group who may benefit from any effect of therapeutic ultrasound.

Outcome measures

In light of advice from the Trial Steering Committee (20 January 2006) and the Trial Management Group (3 March 2006) we decided to amend the primary outcome measure.

The rationale for this was that we had initially set the primary outcome measure as 'complete healing of all ulcers'. This is, clinically, the time at which leg ulcer treatment can be said to have achieved its ultimate aim, and the patient no longer requires dressings, bandages or nurses visits. However, in this trial the ultrasound was to be delivered only to the reference (i.e. largest) ulcer and, therefore, any outcome measure which relied on the healing of other ulcers remote from this would have the potential to dilute any treatment effect.

We therefore amended the primary outcome as 'complete healing of the ulcer treated with ultrasound (the reference ulcer)' and recorded the time to complete healing of all ulcers as a secondary outcome measure.

Digital images

The original protocol did not require the use of digital photographs of the reference ulcer to follow healing progress or to verify healing. However, following the success of this in VenUS II⁴⁴ it was decided to include such digital photographs, to be taken every 4 weeks, on healing and 7 days post healing in order to validate the outcome of healing. These photographs were to be assessed 'blind' by assessors for confirmation of healing.

Questionnaire response rate

We had identified that the patient questionnaire return rates in the previous VenUS trials^{7,44} could be improved and, therefore, we obtained agreement from collaborators and the Ethics Committee to send £5 as a token 'thank you' payment to patients at the end of the trial, with the final questionnaire. This was not mentioned in the patient information sheet, so that any possibility that it would be interpreted as a financial incentive to taking part in the trial was minimised. The final questionnaire, at 12 months post randomisation, was preceded by a letter notifying the patient that their final trial questionnaire was due to arrive shortly. This letter also stated that the questionnaire would be accompanied by a £5 note as a thank you for their taking part in the trial and completing the questionnaires. In the letter it was made explicit that the £5 was not conditional on the patient returning the questionnaire. This approach was based on the results of a systematic review which had investigated ways of increasing questionnaire response rates⁵⁴ and on its successful use in two previous studies co-ordinated by the York Trials Unit.^{73,74}

Chapter 4

Clinical results

This chapter presents the statistical analysis of the clinical results of VenUS III. In the first section of the chapter the clinical data are described, including tables and figures of the data summaries. In the second section the statistical models fitted to the data are presented. Before the results of each statistical model, exploratory data analysis specific to that modelling framework will be presented to show the rationale for this modelling framework.

Trial recruitment

Twelve centres participated in the study from across the UK and Ireland. The number of patients recruited per site ranged from 2 to 102. These were Western Health and Social Care Trust

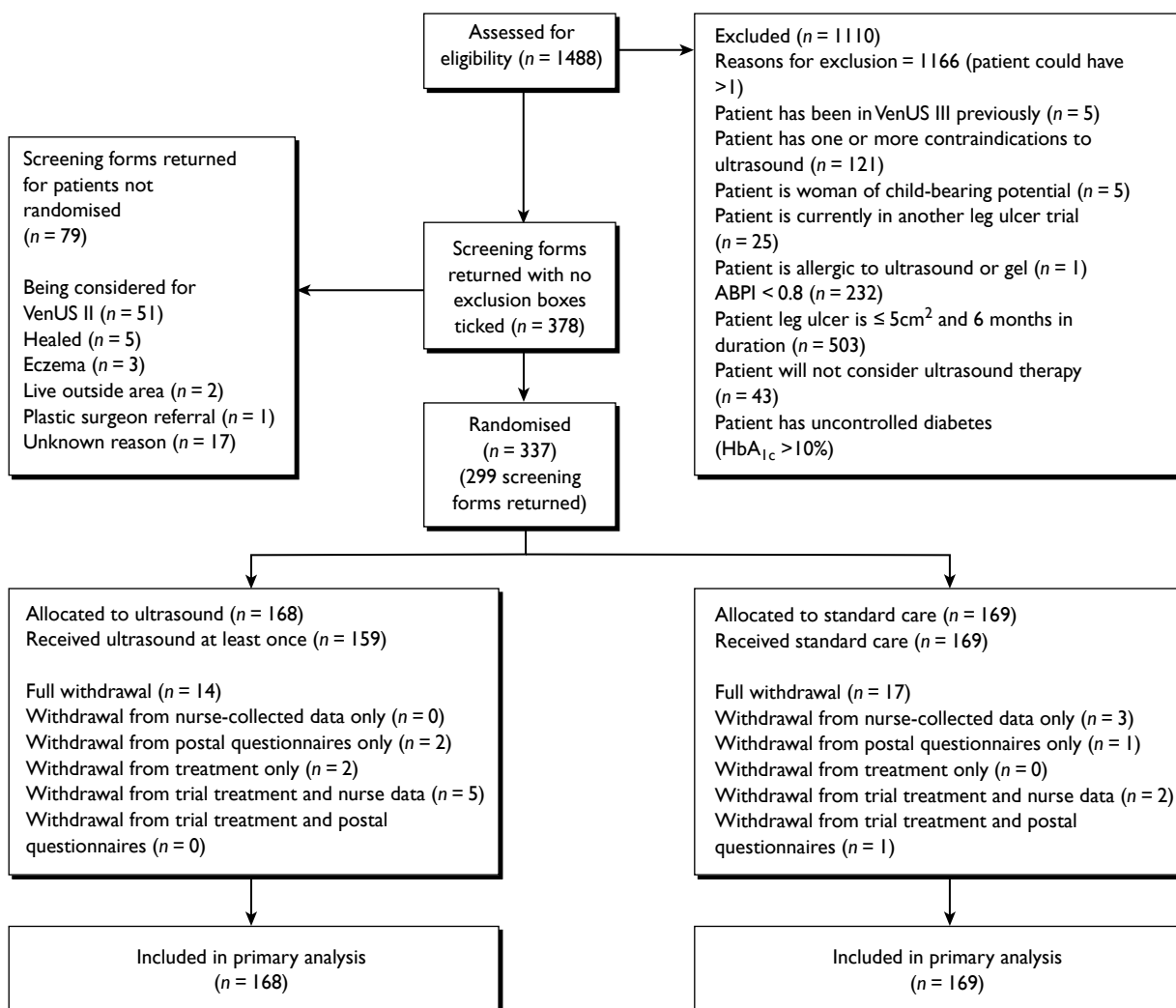


FIGURE 1 Venous Ulcer Study III consolidated standards of reporting trials diagram.

(WHSCCT), Leeds Community, Scarborough, Bradford, Bolton, Nottingham, Hull, South Essex, Birmingham, Dublin, Cumbria and Dunfermline.

Figure 1, the consolidated standards of reporting trials (CONSORT) flowchart, shows the flow of patients through the trial.

Clinical data

Baseline patient characteristics

In total, 337 patients were recruited to the study: 168 in the ultrasound group and 169 in the standard care group. The baseline characteristics are shown in Table 6.

The majority of patients in the study were female (59%) and the two groups were well balanced for gender: 52% females in the ultrasound versus 48% in the control arm. The mean age of the patients in the study was 69 (SD 15) years, and randomisation resulted in well balanced groups for age, gender, body mass index (BMI), and mobility.

TABLE 6 Patient characteristics

	Ultrasound (<i>n</i> =168)	Standard care (<i>n</i> =169)	Overall (<i>N</i> =337)
Gender			
Male (%)	64 (46.72)	73 (53.28)	137 (40.65)
Female (%)	104 (52.00)	96 (48.00)	200 (59.35)
Age (years)			
Mean (SD)	68.91 (14.80)	69.92 (14.21)	69.44 (14.50)
Median (min, max)	71.64 (26.66, 95.76)	71.91 (20.57, 98.81)	71.85 (20.57, 98.81)
Missing (%)	0 (0)	0 (0)	0 (0)
Height (m)			
Mean (SD)	1.69 (0.11)	1.69 (0.11)	1.69 (0.11)
Median (min, max)	1.68 (1.40, 1.96)	1.68 (1.40, 2.01)	1.68 (1.40, 2.01)
Missing (%)	5 (2.98)	5 (2.96)	10 (2.97)
Weight (kg)			
Mean (SD)	86.88 (23.81)	88.71 (27.44)	87.80 (25.66)
Median (min, max)	82.23 (38.10, 180.98)	85.50 (38.10, 184.16)	82.55 (38.10, 184.16)
Missing (%)	6 (3.57)	7 (4.14)	13 (3.86)
BMI			
Mean (SD)	30.42 (7.50)	30.72 (8.28)	30.57 (7.89)
Median (min, max)	28.98 (17.19, 57.01)	29.38 (15.36, 65.53)	29.28 (15.36, 65.53)
Missing (%)	7 (4.17)	8 (4.73)	15 (4.45)
Patient mobility			
Walks freely (%)	90 (48.65)	95 (51.35)	185 (54.90)
Walks with difficulty (%)	69 (48.94)	72 (51.06)	141 (41.84)
Immobile (%)	5 (71.43)	2 (28.57)	7 (2.10)
Missing (%)	4 (2.38)	169 (0.00)	4 (1.19)

max, maximum; min, minimum.

Table 7 shows the baseline ulcer data for both groups. This confirms the chronic, 'hard-to-heal' nature of this population. Ulcer duration was high, as expected with the inclusion criteria (>6 months duration and/or >5 cm²), with a median of 12 months. Median ulcer area was 12 cm² (mean 28 cm²). The median worst ulcer pain score in the previous 24 hours baseline was 31 (range 0–100). The groups were well balanced for ulcer area, duration and level of pain.

The distribution of baseline ulcer area was highly skewed (coefficient of variation 157%); therefore, to reduce this high variability, in the subsequent analysis the logarithm of baseline ulcer area was used. The baseline ulcer duration was also highly skewed (coefficient of variation of 185%) therefore the logarithm of ulcer duration was used.

Table 7 also shows that the two groups are similar in terms of ulcer history on the affected leg, number of previous ulcer episodes, time since first ulcer on this leg and ankle mobility. There seemed to be no difference between the two treatment arms in the distribution of patients in high compression, the mean ABPI, the median duration of the oldest ulcer and number of ulcers per participant. The median number of ulcer episodes was 1.5 (range: 0–99), and the majority of the patients' ankles were described as having a full range of motion (63%); only 3% of patients' ankles were described as 'fixed'. The median ankle circumference was 24 cm (range 17–37cm), and the two groups were comparable to each other: ultrasound: 25 (SD 3) and standard care: 25 (SD 3).

TABLE 7 Baseline ulcer data

	Ultrasound (n= 168)	Standard care (n= 169)	Overall (N= 337)
Reference ulcer area categorised			
≤5 cm ² N and (%)	43 (51.19)	41 (48.81)	84 (24.93)
>5 cm ² N and (%)	125 (49.41)	128 (50.59)	253 (75.07)
Reference ulcer area in cm²			
Mean (SD)	27.95 (44.47)	27.18 (41.96)	27.56 (43.17)
Median (min, max)	12.0 (1.0, 268.0)	12.0 (1.0, 283.5)	12.0 (1.0, 283.5)
Reference ulcer duration			
≤6 months, n (%)	42 (42.86)	56 (57.14)	98 (29.08)
>6 months, n (%)	126 (52.72)	113 (47.28)	239 (70.92)
Ulcer duration (months)			
Mean (SD)	32.19 (64.14)	31.82 (53.96)	32.01 (59.17)
Median (min, max)	12.0 (1.0, 516.0)	11.0 (1.0, 360.0)	12.0 (1.0, 516.0)
Worst pain from ulcer in previous 24 hours (VAS: 0–100)			
Mean (SD)	38.16 (29.36)	32.44 (26.72)	35.28 (28.17)
Median (min, max)	34.51 (0.00, 100.00)	27.46 (0.00, 100.00)	30.80 (0.00, 100.00)
Missing (%)	7 (4.17)	6 (3.55)	13 (3.86)
Reference leg			
Left (%)	99 (53.51)	86 (49.49)	185 (54.90)
Right (%)	66 (44.59)	82 (55.41)	148 (43.92)
Missing (%)	3 (1.79)	1 (0.60)	4 (1.19)
Treated with high compression			
Yes (%)	145 (49.49)	148 (50.51)	293 (86.94)
No (%)	23 (52.27)	21 (47.73)	44 (13.06)

continued

TABLE 7 Baseline ulcer data (*continued*)

ABPI			
Mean (SD)	1.06 (0.19)	1.08 (0.21)	1.07 (0.20)
Median (min, max)	1.06 (0.00, 1.69)	1.10 (0.08, 1.64)	1.08 (0.00, 1.69)
Missing (%)	7 (4.17)	3 (1.78)	10 (2.97)
Duration of oldest ulcer (months)			
Mean (SD)	33.93 (66.91)	33.58 (56.38)	33.75 (61.76)
Median (min, max)	12.0 (0.0, 516.0)	11.0 (0.0, 36.0)	12.0 (0.0, 516.0)
Missing (%)	4 (2.38)	4 (2.37)	8 (2.37)
Number of ulcers on reference leg			
Mean (SD)	2.01 (1.59)	1.81 (1.49)	1.90 (1.54)
Median (min, max)	1 (1, 10)	1 (1, 9)	1 (1, 10)
Missing (%)	3 (1.79)	0 (0.00)	3 (0.90)
Number of ulcer episodes			
Mean (SD)	3.55 (5.03)	3.71 (8.88)	3.63 (7.18)
Median (min, max)	2 (0, 30)	1 (0, 99)	1.5 (1, 99)
Missing (%)	7 (4.17)	12 (7.10)	19 (5.64)
Ankle mobility			
Full range of motion (%)	112 (53.08)	99 (46.92)	211 (62.61)
Reduced range of motion (%)	38 (41.30)	54 (58.70)	92 (27.30)
Fixed ankle (%)	6 (60.00)	4 (40.00)	10 (2.97)
Missing (%)	12 (7.14)	12 (7.10)	24 (7.12)
Ankle circumference (cm)			
Mean (SD)	24.72 (2.91)	24.56 (3.06)	24.64 (2.99)
Median (min, max)	24.5 (17.0, 36.0)	24.0 (19.5, 37.0)	24.0 (17.0, 37.0)
Missing (%)	7 (4.17)	0 (0.00)	7 (2.08)

max, maximum; min, minimum.

Ulcer healing

Determination of healing date

The time to healing (survival time) of the reference ulcer was defined as the time from the date of randomisation to the date of healing (with healing date decided by two independent, blinded adjudicators looking at photographs of the reference ulcers). Any disagreements were resolved by discussion or referral to a third blinded assessor. If no photographs were available, or if they were unclear, then the date recorded on the Ulcer Healed Form was used. Those patients who were lost to follow-up, withdrew from the study and were followed up until the end of the study without experiencing the event (healing of the reference leg ulcer) were treated as censored observations. Their survival time was the last date they were observed in the study. The explanatory variables – ulcer area, ulcer duration, ulcer compression and participating centre – were recorded at baseline.

The kappa measure of agreement was used to assess the agreement between the two assessors of the blinded photographs as to whether or not the wound had healed. This was also repeated by looking at the agreement between the final decision from the blinded photographs and the nurse's decision on healing status of the patients.

Table 8 shows the data comparing the outcomes from two independent assessors for photographs of 331 ulcers/ulcer sites. Of these, 185 ulcers were deemed by both assessors to be 'not healed' while both agreed that 120 had healed. The assessors disagreed in 26 cases: assessor 1 classified 13 ulcers as healed while assessor 2 did not; similarly, assessor 2 classified 13 ulcers as healed while assessor 1 classified them as not healed. To quantify the strength of this association, the kappa measure of agreement was estimated as 0.84 (standard error 0.03, 95% CI 0.78 to 0.90). This indicates an almost perfect agreement. Where the two assessors disagreed on the date of healing, a third assessor was asked to evaluate the blinded photographs and 13 more patients were found to have healed, bringing the total number of healed patients to 133.

In Table 8 we also summarise the extent to which the nurse decision agreed with the blinded photographs. There was agreement between nurses and the photographic assessment (by two assessors – above) for 164 unhealed and 132 healed ulcers. There was disagreement between the nurse judgement and blindly assessed photographs in 41 cases: in 40 cases, the nurse judged that ulcers had healed but the blinded assessors considered the same photographs to indicate that ulcers had not yet healed. In one case the nurse described the ulcer as not healed when the two independent assessors agreed that it had. To quantify the strength of this association the kappa measure of agreement was estimated as 0.76 (standard error 0.03, 95% CI 0.69 to 0.83). This indicates a substantial agreement.

Healing data by site and treatment group

Twelve centres participated in the study (Table 9). In our analysis, centres that recruited fewer than five patients were combined. Consequently, Dunfermline, Cumbria and Dublin were combined with a total enrolment of nine patients (2.67%).

In total, 133 out of the 337 patients (39%) had a healed reference ulcer during follow-up while 204 out of the 337 patients (61%) did not heal. The percentage of healed patients in each centre was highest in WHSCT (57%) and Leeds Community (50%). The number of adverse events (serious or non-serious) by trial centre is given in Table 8. There were a total of 533 adverse events (88 SAEs and 445 NSAEs).

Health-related quality of life data

The SF-12v2 (4-week recall) questionnaire was used to assess self-reported HRQoL at baseline and at 3, 6, 9 and 12 months. The descriptive statistics for the physical component score (PCS) and mental component score (MCS) are presented in Table 10. The descriptive statistics for the other component scores (physical functioning, role physical, bodily pain, general health, vitality, role emotional, social functioning and mental health) are presented later. Analysis was done only

TABLE 8 Results of the blinded classification of healing status using photographs by the two independent assessors (case I) and results of the classification of healing status using blinded photographs and nurse's decision (case II)

		Case I					Case II		
		Assessor 2					Blinded photographs		
		Not healed	Healed	Total			Not healed	Healed	Total
Assessor 1	Not healed	185	13	198	Nurse decision	Not healed	164	1	165
	Healed	13	120	133		Healed	40	132	172
Total		198	133	331	Total	204	133	337	

TABLE 9 Number of patients recruited by treatment group and trial centre

Centre name	Ultrasound (n= 168) (%)	Standard care (n= 169) (%)	Overall N= 337 (%)	Percentage healed	Adverse events: total (NSAE, SAE)
WHSCT	50 (49)	52 (51)	102 (30.27)	57 (58/102)	38 (27, 11)
Leeds Community	22 (50)	22 (50)	44 (13.06)	50 (22/44)	109 (101, 8)
Scarborough	21 (49)	22 (51)	43 (12.76)	47 (20/43)	129 (100, 29)
Bradford	22 (52)	20 (48)	42 (12.46)	33 (14/42)	73 (62, 11)
Bolton	19 (53)	17 (47)	36 (10.68)	19 (7/36)	10 (3, 7)
Nottingham	15 (50)	15 (50)	30 (8.90)	17 (5/30)	51 (40, 11)
Hull	8 (50)	8 (50)	16 (4.75)	31 (5/16)	111 (103, 8)
South Essex	5 (56)	4 (44)	9 (2.67)	0 (0/9)	0 (0, 0)
Birmingham	3 (50)	3 (50)	6 (1.78)	17 (1/6)	7 (6, 1)
Dublin	2 (50)	2 (50)	4 (1.19)	11 (1/9)	5 (3, 2)
Cumbria	1 (33)	2 (67)	3 (0.89)	11 (1/9)	5 (3, 2)
Dunfermline	1 (50)	1 (50)	2 (0.59)	11 (1/9)	5 (3, 2)

on the PCS and MCS. All the other scores have been presented descriptively. The minimum score was 0 and the maximum score was 100, with 0 as the worst score.

The mean PCS and MCS for the study population at baseline were compared with the SF-12v2 standard norms from the 1998 general US population. The median age of the VenUS III population was 72 years so we compared the mean baseline scores of the participants with the US norm-based scores for individuals aged between 65 and 74 years. In VenUS III the PCS means (SD) were 36.55 (11.32) for the ultrasound group and 35.33 (11.47) for the standard care group, compared with 43.93 (9.29) for the general US population. For the MCS, the baseline means were 46.72 (11.52) for the ultrasound group and 47.11 (11.29) for the standard care group, compared with 51.57 (8.36) for the general US population. Therefore, mean PCS and MCS for our trial population were lower than the mean values of the general US population, suggesting that our trial participants had lower QoL in terms of physical and mental health compared with a similar age group in the USA.

The changes in HRQoL as measured by the SF-12v2 are summarised in *Table 10*, and illustrated in *Figures 2* and *3*.

Overall there seemed to be no change in the PCS or the MCS during follow-up. The eight individual subscales of SF-12v2 are shown in *Table 11*.

Record of patient treatment

Table 12 summarises the treatment details of the two groups: for the standard care patients during follow-up and for the ultrasound patients during both the 12 weeks on ultrasound therapy and the post-ultrasound period. For the standard care patients during follow-up, the median number of nurse consultations during study follow-up was 28 (range 1–354). There were a total of 6508 consultations in the home, leg ulcer clinic, nursing home, GP surgery, leg ulcer club and other specified locations. The majority of consultations took place in the leg ulcer clinic (39%), while the fewest were in a leg ulcer club (0.02%). In 40% of consultations knitted viscose dressings were applied (e.g. non-adherent). There were a total of 6473 bandages used during follow-up ranging from four-layer high-compression to non-compressive regimens. The four-layer high-compression system was most frequently applied (35% of consultations).

TABLE 10 Short Form questionnaire-12 items (v2) PCS and MCS

	PCS				MCS				
	Ultrasound (n = 168)	Standard care (n = 169)	Overall (N = 337)	Ultrasound (n = 168)	Standard care (n = 169)	Overall (N = 337)	Ultrasound (n = 168)	Standard care (n = 169)	Overall (N = 337)
	160	167	327	160	167	327	160	167	327
Baseline (n)									
Mean (SD)	36.55 (11.32)	35.33 (11.47)	35.93 (11.40)	46.72 (11.52)	47.11 (11.29)	46.92 (11.39)	46.72 (11.52)	47.11 (11.29)	46.92 (11.39)
Median (range)	36.75 (12.15–58.80)	35.78 (7.10–58.05)	36.28 (7.10–58.80)	47.43 (19.85–67.93)	46.94 (18.71–66.14)	47.25 (18.71–67.93)	47.43 (19.85–67.93)	46.94 (18.71–66.14)	47.25 (18.71–67.93)
Missing (%)	8 (4.76)	2 (1.18)	10 (2.97)	8 (4.76)	2 (1.18)	10 (2.97)	8 (4.76)	2 (1.18)	10 (2.97)
3 months									
Mean (SD)	33.87 (11.49)	34.96 (11.39)	34.41 (11.43)	45.95 (12.22)	46.83 (11.38)	46.39 (11.80)	45.95 (12.22)	46.83 (11.38)	46.39 (11.80)
Median (range)	33.24 (5.90–57.49)	33.76 (8.67–58.05)	33.35 (5.90–58.05)	46.36 (12.61–72.78)	48.61 (17.55–68.49)	47.43 (12.61–72.78)	46.36 (12.61–72.78)	48.61 (17.55–68.49)	47.43 (12.61–72.78)
Missing (%)	25 (14.88)	27 (15.98)	52 (15.43)	25 (14.88)	27 (15.98)	52 (15.43)	25 (14.88)	27 (15.98)	52 (15.43)
6 months									
Mean (SD)	34.65 (12.59)	34.93 (12.24)	34.79 (12.39)	46.05 (11.69)	46.83 (10.84)	46.46 (11.25)	46.05 (11.69)	46.83 (10.84)	46.46 (11.25)
Median (range)	33.55 (4.64–59.11)	34.21 (8.37–61.52)	33.97 (4.64–61.52)	48.28 (14.29–66.77)	47.79 (19.75–67.51)	47.85 (14.29–67.51)	48.28 (14.29–66.77)	47.79 (19.75–67.51)	47.85 (14.29–67.51)
Missing (%)	41 (24.40)	34 (20.12)	75 (22.26)	41 (24.40)	34 (20.12)	75 (22.26)	41 (24.40)	34 (20.12)	75 (22.26)
9 months									
Mean (SD)	34.51 (11.81)	34.55 (12.31)	34.53 (12.03)	46.86 (12.42)	46.88 (11.18)	46.87 (11.78)	46.86 (12.42)	46.88 (11.18)	46.87 (11.78)
Median (range)	33.98 (9.43–58.05)	33.45 (10.29–60.18)	33.50 (9.43–60.18)	47.72 (14.48–65.58)	46.92 (15.33–65.20)	47.50 (14.48–65.58)	47.72 (14.48–65.58)	46.92 (15.33–65.20)	47.50 (14.48–65.58)
Missing (%)	52 (30.95)	52 (30.77)	104 (30.86)	52 (30.95)	52 (30.77)	104 (30.86)	52 (30.95)	52 (30.77)	104 (30.86)
12 months									
Mean (SD)	34.61 (12.09)	35.57 (1.88)	35.07 (11.97)	47.51 (11.54)	45.41 (12.15)	46.49 (11.86)	47.51 (11.54)	45.41 (12.15)	46.49 (11.86)
Median (range)	33.19 (8.17–60.39)	35.07 (13.93–57.49)	34.36 (8.17–60.39)	48.50 (15.48–67.69)	44.67 (12.52–71.22)	47.08 (12.52–71.22)	48.50 (15.48–67.69)	44.67 (12.52–71.22)	47.08 (12.52–71.22)
Missing (%)	50 (29.76)	58 (34.32)	108 (32.05)	50 (29.76)	58 (34.32)	108 (32.05)	50 (29.76)	58 (34.32)	108 (32.05)

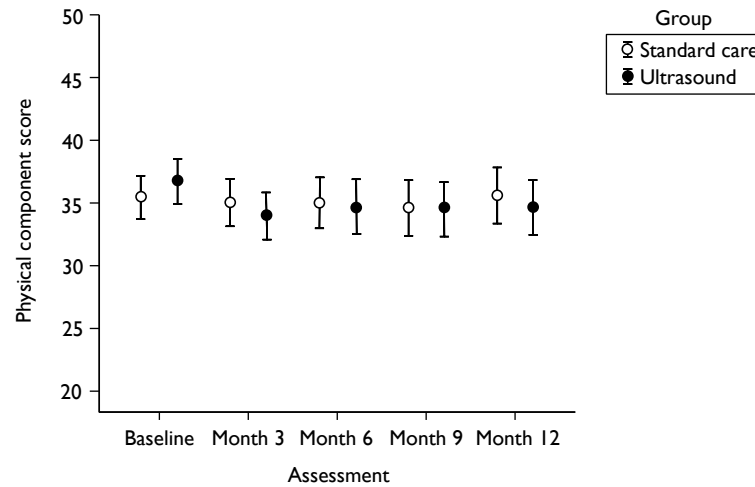


FIGURE 2 Short Form questionnaire-12 items physical component scores over time (mean and 95% CI).

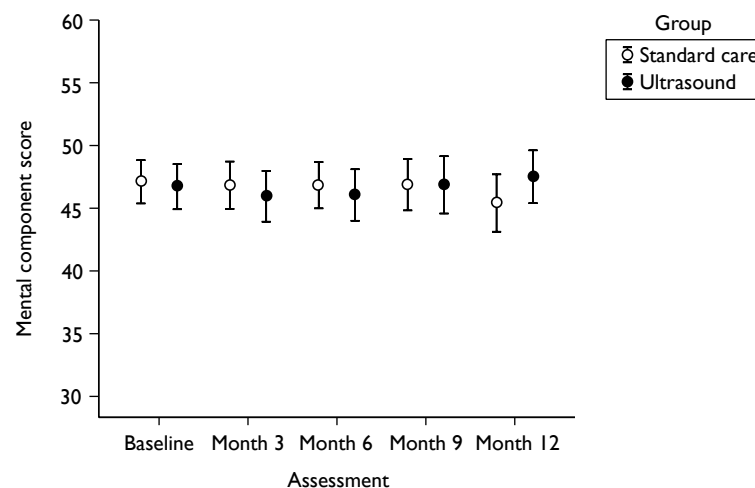


FIGURE 3 Short Form questionnaire-12 items mental component scores over time (mean and 95% CI).

The median number of nurse consultations during the initial 12 weeks of ultrasound therapy was 13 (range 2–51; total of 2412 consultations). The majority of consultations took place at the leg ulcer clinic (45%) and the fewest at a leg ulcer club (0.04%). The median number of ultrasound applications was 11 (range 1–15). Ultrasound was delivered during most treatment consultations during the initial 12-week period: the median proportion of visits receiving ultrasound was 0.86 (range 0.14–1). In total, patients received more than 1 hour of ultrasound: the median duration of total ultrasound application was 69 minutes (range 9–130). During the post-ultrasound therapy period, the median number of nurse consultations was 33 (range 1–273) mainly in leg ulcer clinics (38%) with no consultations in leg ulcer clubs (0%). Knitted viscose dressings were applied during 40% of these consultations while three-layer high compression was applied in 33%.

TABLE 11 Short Form questionnaire-12 items (v2) standard recall physical and mental scores

Time point	Physical scores, mean (SD)			Mental scores, mean (SD)		
	Ultrasound (n= 168)	Standard care (n= 169)	Overall (N= 337)	Ultrasound (n= 168)	Standard care (n= 169)	Overall (N= 337)
	Physical functioning			Vitality		
Baseline	36.54 (11.62)	36.23 (12.15)	36.38 (11.88)	44.16 (11.36)	43.05 (12.44)	43.60 (11.92)
3 months	34.28 (11.94)	34.81 (12.54)	34.54 (12.23)	42.26 (11.56)	43.00 (11.03)	42.63 (11.29)
6 months	34.27 (11.98)	34.81 (12.34)	34.55 (12.14)	41.73 (10.48)	42.64 (10.74)	42.20 (10.61)
9 months	34.23 (12.21)	34.74 (12.20)	34.48 (12.18)	42.46 (10.98)	42.85 (11.41)	42.65 (11.18)
12 months	34.69 (12.49)	34.85 (12.37)	34.76 (12.40)	42.25 (10.78)	42.44 (10.97)	42.34 (10.84)
	Role physical			Social functioning		
Baseline	39.01 (11.85)	34.70 (11.21)	38.35 (11.53)	39.61 (14.47)	39.09 (14.34)	39.49 (14.39)
3 months	37.53 (11.67)	38.36 (11.40)	37.94 (11.52)	37.57 (14.46)	40.10 (13.94)	38.83 (14.23)
6 months	37.86 (11.32)	37.93 (10.89)	37.90 (11.07)	38.28 (14.44)	39.76 (13.62)	39.04 (14.01)
9 months	38.39 (10.96)	37.68 (11.50)	38.04 (11.22)	39.24 (14.70)	39.65 (13.71)	39.45 (14.18)
12 months	38.57 (11.18)	39.08 (10.95)	38.82 (11.05)	39.20 (14.09)	38.74 (13.95)	38.97 (13.99)
	Bodily pain			Role emotional		
Baseline	38.60 (14.05)	38.52 (13.53)	38.56 (13.77)	42.99 (13.08)	44.10 (12.69)	43.55 (12.87)
3 months	36.41 (13.53)	38.57 (12.84)	37.49 (13.21)	41.52 (14.10)	42.84 (12.79)	42.18 (13.45)
6 months	38.02 (14.15)	38.95 (13.36)	38.49 (13.73)	42.93 (13.49)	43.24 (12.09)	43.09 (12.77)
9 months	38.65 (12.92)	38.29 (13.91)	38.47 (13.40)	42.53 (13.56)	42.09 (13.36)	42.31 (13.43)
12 months	38.55 (13.79)	38.54 (12.49)	38.55 (13.14)	43.11 (13.78)	41.37 (12.85)	42.27 (13.33)
	General health			Mental health		
Baseline	40.50 (11.90)	39.30 (12.41)	39.88 (12.02)	46.32 (11.40)	46.40 (10.82)	46.36 (11.09)
3 months	37.23 (11.77)	37.91 (11.25)	37.56 (11.50)	46.13 (12.05)	45.91 (10.96)	46.02 (11.50)
6 months	38.27 (12.09)	37.94 (12.04)	38.10 (12.04)	45.37 (11.80)	46.01 (11.06)	45.70 (11.41)
9 months	37.47 (11.93)	37.93 (11.33)	37.70 (11.61)	46.73 (12.04)	46.78 (10.70)	46.75 (11.36)
12 months	38.57 (11.99)	37.82 (12.21)	38.21 (12.08)	47.91 (10.95)	45.60 (12.17)	46.79 (11.59)

Analysis of clinical results

This portion of the report presents the results of the statistical models fitted to the data. It is arranged into three main sections as follows. The first section presents the results of the modelling of the primary outcome: time to healing of the reference leg ulcer. The second section presents the results of the modelling of the secondary outcomes: ulcer areas, QoL, complete healing of all ulcers at 12 months, ulcer recurrence and adverse events. The third section presents the conclusions of the statistical analysis of the clinical outcomes.

Modelling of the primary outcome (time to healing of leg ulcers)

The primary analysis compared the time to healing of the reference ulcer between the two randomised groups: ultrasound plus standard care and standard care alone. This was accomplished by fitting a Cox proportional hazard regression model with the main covariate as treatment adjusting for baseline ulcer area, baseline ulcer duration, ulcer compression and centre.

As seen in *Table 9*, the number of patients healing in each centre varied. We assumed that the 10 centres in this study were a random sample drawn from a population of centres on which we would like to make inferences. Therefore, centre was treated as a random effect in the Cox proportional hazard regression (shared-frailty effect). Observations from the same centre share

TABLE 12 Treatment details

Group	Standard care (n= 169)	Ultrasound (n= 168)	
	Through trial follow-up	Initial 12 weeks of ultrasound	Post 12 weeks' ultrasound
Number of nurse consultations			
Mean (SD)	41.34 (46.76)	15.36 (8.88)	39.23 (38.06)
Median (min, max)	28 (1, 354)	13 (2, 51)	33 (1, 273)
Missing (%)	10 (5.92)	9 (5.34)	47 (27.98)
Setting of treatment consultation			
Home (%)	2344 (36.02)	817 (33.87)	1717 (36.45)
Leg ulcer clinic (%)	2545 (39.11)	1077 (44.65)	1806 (38.34)
Nursing home (%)	13 (0.20)	20 (0.83)	29 (0.62)
GP surgery (%)	1071 (16.46)	324 (13.43)	783 (16.62)
Leg ulcer club (%)	1.0 (0.02)	1 (0.04)	0 (0.00)
Other (%)	534 (8.21)	173 (7.17)	375 (7.96)
Total (%)	6508 (100)	2412 (100)	4710 (100)
Knitted viscose dressing applied			
Yes (%)	2556 (39.86)	1181 (54.55)	1889 (40.33)
No (%)	3856 (60.14)	984 (45.45)	2795 (59.67)
Total (%)	6412 (100)	2165 (100)	4684 (100)
Compression bandages applied			
Four-layer high compression (%)	2241 (34.62)	875 (36.83)	1276 (22.64)
Three-layer high compression (%)	1543 (23.84)	488 (20.54)	1837 (32.59)
Three-layer reduced compression (%)	668 (10.32)	188 (7.91)	875 (15.52)
Two-layer high compression (%)	857 (13.24)	297 (12.50)	624 (11.07)
Short-stretch compression (%)	805 (12.44)	319 (13.43)	529 (9.38)
Low compression (%)	139 (2.15)	82 (3.45)	168 (2.98)
No compression (%)	220 (3.40)	127 (5.35)	328 (5.82)
Total (%)	6473 (100)	2376 (100)	5,637 (100)
Number of ultrasound applications			
Mean (SD)	–	10.25 (2.96)	–
Median (min, max)	–	11 (1, 15)	–
Missing (%)	–	9 (5.34)	–
Proportion of consultations where ultrasound applied			
Mean (SD)	–	0.77 (0.24)	–
Median (min, max)	–	0.86 (0.14, 1.00)	–
Missing (%)	–	9 (5.34)	–
Duration of ultrasound application (minutes)			
Mean (SD)	–	73.94 (31.69)	–
Median (min, max)	–	69.0 (9.0, 130.0)	–
Missing (%)	–	9 (5.34)	–

max, maximum; min, minimum.

the same frailty effect. Hence, observations from the same centre are correlated because they share the same frailty effect. The frailty effect is a latent random effect that enters multiplicatively on the hazard function.

Figure 4 shows that there was a high level of variability in the healing rates between centres, with patients from WHSCT seemingly more frail (healing more) than patients from other centres. Similarly, patients from South Essex were seemingly less frail (healed less) than those from other centres. No patients healed from South Essex. There was a significant difference in the survival time among centres (log-rank test 36.19, $p < 0.0001$) unadjusted for other covariates in the model. This variability in the healing rates between centres will be accounted for by including a centre frailty effect in the model. So patients from the same centre are correlated because they share the same frailty effect.

There was no evidence of a difference in survival (time to healing) between the two treatment groups using the log-rank statistic (0.2544, $p = 0.6140$) and the Wilcoxon test (0.3350, $p = 0.5628$) (Figure 5). In other words, we have identified no evidence that low-dose ultrasound significantly affects the time to healing of hard-to-heal venous leg ulcers.

Table 13 shows the median time to healing and lower boundary of the 95% CI. Note that the upper 95% CI could not be estimated from the data because fewer than half the patients in each group healed (64 out of 168 patients in the ultrasound group and 69 out of 169 in the standard care group).

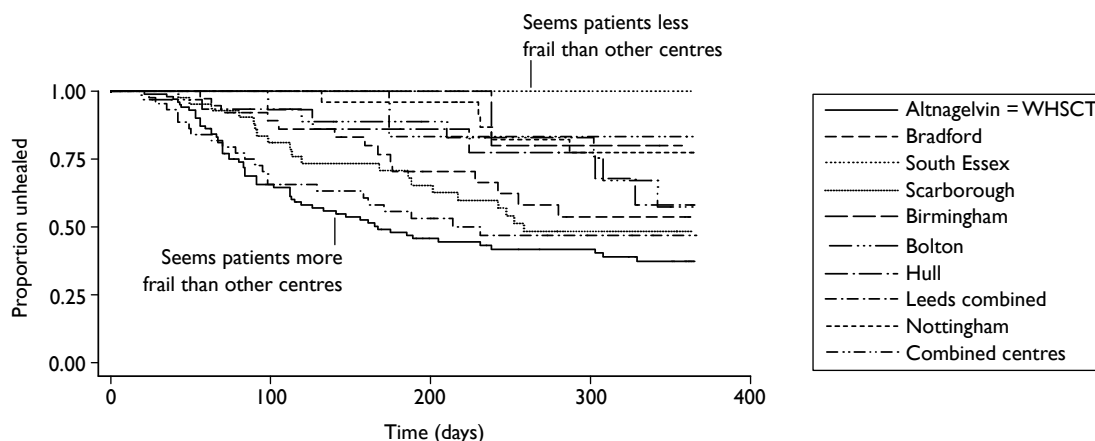


FIGURE 4 Unadjusted Kaplan–Meier survival curves by participating centre showing high variability in healing rates between centres.

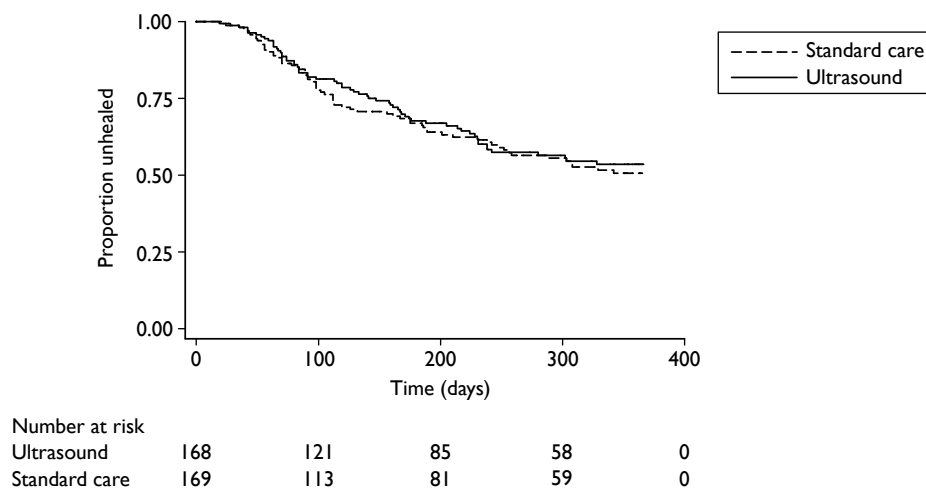


FIGURE 5 Unadjusted Kaplan–Meier survival curves by treatment randomised.

TABLE 13 Unadjusted Kaplan–Meier survival estimates and the log-rank test of the equality of the two survival curves

Number of adverse events	Ultrasound (<i>n</i> = 168)	Standard care (<i>n</i> = 169)
Number healing/total number healed (%)	64/133 (48)	69/133 (52)
<i>Unadjusted Kaplan–Meier estimates</i>		
Median time to healing (days, 95% CI)	Inestimable (238, inestimable)	Inestimable (252, inestimable)
Log-rank test statistic; (<i>p</i> -value)	0.2544 (<i>p</i> = 0.6140)	
Wilcoxon test statistic; (<i>p</i> -value)	0.3350 (<i>p</i> = 0.5628)	

The results of fitting the Cox proportional hazard regression model without and with the centre frailty parameter are given in *Table 14*. For the model without the frailty effect, the hazard ratio of ultrasound versus standard care is 1.01 ($p = 0.9520$) adjusting for log(area), log(duration) and ulcer compression. There was no evidence that the survival experience (healing time) of patients randomised to ultrasound and standard care is different. The hazard ratio for log(area) is 0.66 ($p < 0.0001$) adjusting for treatment, log(duration) and ulcer compression. Therefore, there was a significant effect of area on the healing time experience of both groups in that small ulcers healed more quickly than large ulcers. The hazard ratio for log(duration) was 0.57 ($p < 0.0001$) adjusting for treatment, log(area) and ulcer compression. Therefore, there was a significant effect of log(duration) on the time to healing for all patients in that newer ulcers healed faster than older ulcers. The hazard ratio for compression versus no compression was 0.93 ($p = 0.7740$). Therefore, there was no effect of compression usage at baseline on the survival experience of the patients in the two arms of the study.

The proportional hazard (PH) assumption assumes that the hazard ratios above do not depend on time (i.e. they are constant over time). This assumption was tested via a statistical test on each covariate separately then globally over all the four covariates in the model. The idea behind this test is that if the PH assumption is valid then the Schoenfeld residuals for the global test and Schoenfeld scaled residuals for separate tests with each covariate should not be correlated with survival time. If, on the other hand, the residuals tend to be positive for subjects who heal at relatively earlier time and negative for subjects who heal at a relatively late time (or vice versa) then there is evidence that the hazard ratio is not constant over time (i.e. PH assumption is violated).⁷⁵ The test of the PH assumption was insignificant (ultrasound vs standard care, $p = 0.8677$; log(area), $p = 0.1147$; log(duration), $p = 0.2914$; high compression, $p = 0.1270$; and global test, $p = 0.2548$) meaning that the PH assumption was not violated separately for each covariate and globally for all covariates. Hence, the hazard ratios were assumed to be constant over time.

For the model with the centre frailty effect, there was a significant centre frailty effect ($p < 0.0001$), meaning that the correlation of patients within a study centre could not be ignored. All hazard ratios have the same interpretation, but conditioned on centre (i.e. compares patients from the same centre). The hazard ratio of ultrasound versus standard care was 0.99 ($p = 0.9690$) adjusting for log(area), log(duration) and ulcer compression for patients from the same study centre.

In the estimation of the centre frailty effect, the significance of the centre frailty effect was tested under the null hypothesis that its variance was equal to zero (centre frailty effects were assumed to be distributed as gamma random variables with mean 1 and variance theta). So the null hypothesis is on the boundary of the parameter space (as variances can never be negative); hence the null distribution of the likelihood ratio test statistic is not just a chi-squared [degrees of freedom (df): 1], but a 50:50 mixture of chi-squared (df0), point mass at 0 and a chi-squared (df1). As such, the *p*-value was calculated from a mixture of these two chi-squared distributions.

TABLE 14 Cox proportional hazard regression of time to healing versus treatment adjusting for baseline ulcer area, duration and compression without and with the shared centre frailty parameter

Parameter	Estimate (standard error)	Hazard ratio (95% CI)	p-value	Test of PH assumption p-value
Without centre frailty effect				
Ultrasound vs standard care	0.01 (0.16)	1.01 (0.72 to 1.43)	0.9520	0.8677
Log(area)	-0.41 (0.08)	0.66 (0.57 to 0.77)	0.0001	0.1147
Log(duration)	-0.56 (0.09)	0.57 (0.48 to 0.68)	0.0001	0.2914
High compression (yes vs no)	-0.07 (0.24)	0.93 (0.58 to 1.49)	0.7740	0.1270
Global test of PH assumption	-	-	-	0.2548
With centre frailty effect				
Ultrasound vs standard care	-0.01 (0.18)	0.99 (0.70 to 1.40)	0.9690	0.7230
Log(area)	-0.44 (0.08)	0.64 (0.55 to 0.75)	0.0001	0.1467
Log(duration)	-0.51 (0.09)	0.59 (0.50 to 0.71)	0.0001	0.2938
High compression (yes vs no)	-0.10 (0.25)	0.90 (0.56 to 1.46)	0.673	0.2030
Theta	0.26 (0.20)	-	-	-
Global test of PH assumption	-	-	-	0.3536

Test of significance of frailty parameter: $H_0: \theta = 0$ [chi-squared (degrees of freedom 01) 12.78, $p < 0.0001$].

Note: in the model with centre frailty effect standard errors of hazard ratios are conditional on theta.

Similarly, as before, the PH assumption was tested here. The results show that the assumption was not violated separately for each covariate [ultrasound vs standard care, $p = 0.7230$; log(area), $p = 0.1467$; log(duration), $p = 0.2938$; high compression, $p = 0.2030$; or globally, $p = 0.3548$]. Comparing the models without and with the centre frailty effect we can see that the results are similar; however, the advantage of the model with the centre frailty effect is that it takes into account the fact that participants within each study centre are highly correlated.

Analysis of secondary outcomes

In this section, the results of the secondary analysis of ulcer area, QoL, complete healing of all ulcers at 12 months, rates of ulcer recurrence and finally adverse events are presented.

Ulcer area

Previous research has shown that the initial reduction in ulcer area (percentage reduction after 4 weeks of good wound care) is predictive of eventual healing.⁴⁵ Therefore, we compared the initial healing rates between the ultrasound and standard care groups. The ulcer area at week 4 was compared between treatment groups using a linear mixed model to adjust for baseline ulcer area, centre, ulcer duration and use of compression. The model is linear because we have a continuous response and mixed because we have fixed effects (baseline ulcer area, ulcer duration and use of compression) and a random effect (centre).

The mean ulcer area at baseline was 27.56 cm² (SD 43.17 cm²). The median was 12.0 cm² (range 1.0–283.5 cm²). The mean ulcer area after 4 weeks was 22.65 cm² (SD 43.14 cm²), median 8.00 cm² (range 0.11–368.50 cm²). There seemed to be a reduction in the mean and median ulcer area after 4 weeks. The ulcer area at 4 weeks was modelled as the response variable and the main covariate in the model was the treatment group randomised adjusted for baseline ulcer area, centre, ulcer duration and use of compression.

The results in *Table 15* show that there was a non-significant treatment effect (0.05, $p = 0.4979$) and a non-significant ulcer compression effect (0.02, $p = 0.8361$). There was a significant

TABLE 15 Parameter estimates (standard errors), p -values and 95% CIs of the linear mixed model of log (week 4 baseline ulcer area) as response with treatment, baseline ulcer area, baseline ulcer duration and use of compression as fixed effects and centre as a random effect

Parameter	Estimate (standard error)	p -value	95% CI
Fixed effects			
Intercept	-0.02 (0.15)	0.8752	-0.33 to 0.28
Ultrasound vs standard care	0.05 (0.07)	0.4979	-0.09 to 0.19
Baseline log(area)	0.77 (0.03)	0.0001	0.72 to 0.84
Baseline log(duration)	0.13 (0.03)	0.0001	0.07 to 0.19
Ulcer compression (yes vs no)	0.02 (0.11)	0.8361	-0.19 to 0.24
Covariance parameters			
Random centre effect	0.01 (0.01)	0.1489	-
Measurement error	0.39 (0.03)	0.0001	-

baseline log(area) effect (0.77, $p=0.0001$) and baseline log(duration) effect (0.13, $p=0.0001$). Therefore, there was no evidence that therapeutic low-dose ultrasound significantly increased the rate of change of venous ulcer area over the first 4 weeks of treatment and no evidence that the application of compression significantly influenced the rate of change of ulcer area over 4 weeks. As there was a significant log(area) effect, then for a unit increase in baseline log(area), the log(area) at week 4 increases by 0.77 cm² (95% CI 0.72 to 0.84 cm²). Similarly, for the log(duration) effect there was an increase of 0.13 cm² (95% CI 0.07 to 0.19 cm²) in log(area) after 4 weeks for each unit increase in log(duration) at baseline. After adjusting for the other covariates in the model, there was a non-significant centre random effect (0.01, $p=0.1489$). So log(area) scores after 4 weeks did not significantly vary among centres.

Complete healing of all ulcers at 12 months

The number of leg ulcers that had completely healed by 12 months was based on nurse-reported data and not on blinded photographs as photographs were not taken after the reference ulcer had healed. After 12 months of follow-up there were 72 patients (48%) in the ultrasound group and 78 patients (52%) in the standard care group whose ulcers had all healed. There is little difference in the proportions of patients with all ulcers healed after 12 months between the two groups.

Kaplan–Meier survival curves for time to healing are shown in *Figure 6*. The median time to complete healing of all ulcers in the standard care group was 328 days (95% CI 235 days, inestimable) and for the ultrasound group was 365 days (95% CI 224 days, inestimable). Under the null hypothesis of no difference in the survival experience of the two groups of patients, the log-rank test ($p=0.6051$) and the Wilcoxon test ($p=0.6357$) were not significant; hence, there was no statistically significant difference in the time to complete healing of all ulcers in the two treatment groups. A formal analysis, such as Cox regression analysis, was not performed here as for the primary outcome as any other ulcers that the patient may have had were not receiving ultrasound treatment.

Ulcer recurrence

Patients were contacted by telephone at 6, 9 and 12 months after healing to ascertain if their healed reference ulcers had recurred. The proportions of patients whose healed reference ulcer had recurred are summarised by treatment group. We were able to contact 124 patients out of the 133 patients that healed in the study; the remaining patients were not contacted for a variety of reasons including invalid telephone numbers, no telephone number provided, telephone unanswered, patients seemed confused and the patients had moved to a different location.

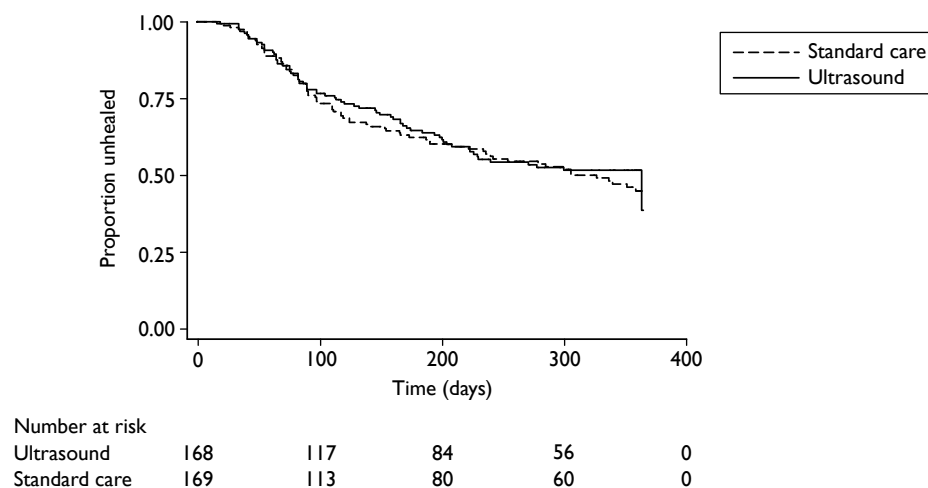


FIGURE 6 Kaplan–Meier plot of time to complete healing of all ulcers by treatment group.

The number of patients whose reference ulcer had recurred was 31 out of 124 (25%), whereas 93 out of 124 (75%) had no reference ulcer recurrence. Of the 31 patients with ulcer recurrence, 14 patients (45%) were in the standard care group, while 17 patients (55%) were in the ultrasound group. There was no statistically significant difference in the recurrence rates between the two groups (Fisher's exact test, $p = 0.6803$).

Quality of life using the Short Form questionnaire-12 items

The HRQoL was measured using the SF-12 questionnaire over time [at baseline (0), 3, 6, 9 and 12 months]. There was very little change in the scores over time (constant linear trend of PCS and MCS against time; see *Figures 2* and *3*). Also, there was no increase in the SDs (constant standard errors) of the mean scores against time of follow-up as seen from the SDs at months 0, 3, 6, 9 and 12. There was high variability in PCS and MCS at baseline so random intercepts were included in the model. Thus, the modelling strategy that was adopted was to fit two linear mixed models with response variables PCS and MCS separately and covariates were treatment, baseline ulcer area, ulcer duration, compression usage, time (0, 3, 6, 9 and 12 months) and an interaction between time and treatment to assess whether QoL scores differed over time for the two treatments. We included centre as a random effect. We used a linear mixed model as time was nested within patients, so there was need to account for within-patient correlation in the PCS and MCS.

Table 16 shows the results of the linear mixed model fitted to the PCS and MCS. In the model with PCS as the response variable there were non-significant effects of ultrasound versus standard care, time, log(area), an interaction between treatment and time and ulcer compression. There was a significant effect of log(duration). There was not enough evidence of a significant difference in the mean PCS scores of the patients between the two treatment groups ($0.69, p = 0.5773$) and there was not enough evidence of a significant difference between the two treatment groups during follow-up ($-0.11, p = 0.1944$). There was not enough evidence of a significant difference in PCS mean scores for patients with different ulcer log(area) at baseline ($-0.81, p = 0.0840$). However, adjusting for all the other covariates in the model, there was a significant effect of log(duration) ($-1.22, p = 0.0145$). This implies that, adjusting for other covariates in the model, there was a 1.22 reduction in mean PCS scores for a unit increase in log(duration). Hence, longer ulcer duration was associated with lower mean PCS scores than was shorter ulcer duration. There was a borderline ulcer compression effect ($3.25, p = 0.0661$). This implies that, adjusting for all other covariates in the model, those who were using compression at baseline had PCS mean scores 3.25 higher than those who were not using compression.

TABLE 16 Parameter estimates (standard errors), *p*-values and 95% CIs of the linear mixed models fitted to the PCS and the MCS

Parameter	PCS			MCS		
	Estimate (standard error)	<i>p</i> -value	95% CI	Estimate (standard error)	<i>p</i> -value	95% CI
Fixed effects						
Intercept	38.14 (2.45)	0.0001	36.73 to 44.59	49.83 (2.22)	0.0001	46.45 to 54.20
Treatment (ultrasound vs standard care)	0.69 (1.23)	0.5773	-1.79 to 3.08	-0.93 (1.21)	0.4395	-3.30 to 1.44
Time	-0.03 (0.06)	0.6657	-0.15 to 0.09	-0.10 (0.07)	0.1760	-0.24 to 0.04
Log(area)	-0.81 (0.46)	0.0840	-1.72 to 0.10	-0.13 (0.43)	0.7702	-0.97 to 0.72
Log(duration)	-1.22 (0.49)	0.0145	-2.12 to -0.17	-1.00 (0.46)	0.0312	-1.91 to -0.09
Treatment × time	-0.11 (0.09)	0.1944	-0.29 to 0.06	0.16 (0.10)	0.1249	-0.04 to 0.36
Ulcer compression (yes vs no)	3.25 (1.76)	0.0661	-0.22 to 6.71	0.23 (1.63)	0.8860	-2.97 to 3.44
Covariance parameters						
Random intercept	94.96 (8.90)	0.0001	–	80.56 (7.99)	0.0001	–
Centre	3.77 (3.92)	0.1681	–	0.28 (1.26)	0.4125	–
Autoregressive	0.30 (0.05)	0.0001	–	0.15 (0.05)	0.0040	–
Measurement error (residual variance)	37.24 (2.67)	0.0001	–	53.17 (3.02)	0.0001	–

As much of the variation in the data was at baseline, this was modelled through random intercepts. This means that each individual patient's baseline intercept varies around an average value of 38.14 ($p=0.0001$) with the total random intercept variation estimated as 94.96 ($p=0.0001$). This implies that there were baseline differences that needed to be accounted for in the data, and this was adequately modelled by using random intercepts. The centre effect entered the model as a random effect. The estimate of the variance of the centre effect was 3.77 ($p=0.1681$). This implies that after adequately modelling the data, adjusting for all the other covariates in the model, the variability in the mean PCS scores between centres was not statistically significant. The correlation between measurements on the same individual was modelled by the autoregressive correlation. This assumes that the measurements close together are highly correlated (i.e. month 0 vs month 3), while measurements far apart are less correlated (i.e. month 0 vs month 6). In other words the correlation decreases as the time lag between measurements increases. The autoregressive correlation estimate was 0.30 ($p=0.0001$), i.e. two measurements from the same subject 3 months apart have a correlation of 0.30. For measurements 6 months apart, the correlation is estimated as $0.30^2=0.09$, and so on. This implied that the correlation between the longitudinal patient's measurements could not be ignored and that it needed to be modelled in the data. To arrive at the autoregressive correlation as the best one here, different correlation structures were compared by the likelihood ratio test, and this correlation structure was the one that increased the likelihood more with respect to the number of parameters in the model. The measurement error was estimated as 37.24 ($p=0.0001$). In conclusion, considering all the random effects in the model, much variability was attributed to differences in baseline PCS scores. No CIs are presented for the covariance parameters.

In the model with MCS as the response variable, there were non-significant effects of ultrasound versus standard care, time, log(area), an interaction between treatment and time and ulcer compression. There was a significant effect of log(duration). This implies that there was no statistically significant difference in the mean MCS scores of the patients between the two

treatment groups ($-0.93, p=0.4395$) and, similarly, there was no statistically significant difference between the two treatment groups during follow-up (with time) ($0.16, p=0.1249$). There was no statistically significant difference in mean MCS scores for patients with different ulcer log(area) at baseline ($-0.13, p=0.7702$). However, adjusting for all the other covariates in the model, there was a significant effect of log(duration) ($-1.00, p=0.0312$). This implies that, adjusting for other covariates in the model, there was a 1.00 reduction in mean MCS scores for a unit increase in log(duration). Hence, longer ulcer duration was associated with lower mean MCS scores than was shorter ulcer duration. There was an insignificant ulcer compression effect ($0.23, p=0.8860$). This implies that, adjusting for all other covariates in the model, there was no statistically significant difference in mean MCS scores between those who were using compression at baseline and those who were not.

As much of the variation in MCS scores was at baseline, this was modelled through random intercepts. This means that each individual patient's baseline intercept varies around an average value of 49.83 ($p=0.0001$), with the total random intercept variation estimated as 80.56 ($p=0.0001$). This implied that there were baseline differences that needed to be accounted for in the data, and this was adequately modelled by using random intercepts. The centre effect was entered into the model as a random effect. The estimate of the variance of the centre effect is 0.28 ($p=0.4125$). This implies that after adequately modelling the data, adjusting for all the other covariates in the model, the variability in the mean MCS scores between centres was not significant. The correlation between measurements on the same individual was modelled by the autoregressive correlation. The autoregressive correlation estimate was 0.15 ($p=0.0001$). This implies that the correlation between the longitudinal patient's measurements could not be ignored and needed to be modelled in the data. Different correlation structures were compared with this by the likelihood ratio test and this correlation structure was the best. The measurement error was estimated as 53.17 ($p=0.0001$). Therefore, in conclusion, as for the PCS scores, considering all the random effects in the model, much variability was attributed to differences in baseline MCS scores.

Adverse events

Here we present the analysis of the adverse events data in the form of descriptive statistics and then random effects negative binomial regression models of the adverse events. To account for the excess zeros (many patients had no adverse events), alternative zero-inflated random effects negative binomial regression models will be considered.

Serious adverse events

There was a total of 88 SAEs in 64 patients. Of these, 29 patients (45%) were in the standard care group and 35 (55%) were in the ultrasound group (*Table 17*). For all the subjects in the study, the mean number of SAEs per patient was 0.26 (SD 0.62). The median number of SAEs was 0.00 (range 0.00–4.00). The coefficient of variation was approximately 238%; hence, there was too much variability in the number of SAEs per patient. The data are overdispersed (i.e. variance much larger than the mean).

Non-serious adverse events

There were 445 NSAEs in 153 patients (45%). Of these patients, 67 (44%) were in the standard care group and 86 (56%) were in the ultrasound group (*Table 17*). Considering all 337 patients in the study, the mean number of NSAEs per patient was 1.32 (SD 2.23). The median number of NSAEs was 0.00 (range 0.00–15.00). The coefficient of variation was approximately 169%; hence, there was relatively too much variability (overdispersion) in the number of NSAEs per patient.

The outcome variables (number of NSAEs, number of SAEs and number of NSAEs and SAEs combined) have been regressed against treatment group, baseline ulcer area, baseline ulcer

TABLE 17 Number of SAEs and NSAEs categorised by the treatment the patient was randomised

	Treatment group		
	Standard care (%)	Ultrasound (%)	Total (%)
Number of SAEs			
0	140 (51.28)	133 (48.72)	273 (81.01)
1	20 (43.48)	26 (56.52)	46 (13.65)
2	9 (64.29)	5 (35.71)	14 (4.15)
3	0 (0.00)	2 (100.00)	2 (0.59)
4	0 (0.00)	2 (0.00)	2 (0.59)
Number of NSAEs			
0	102 (55.43)	82 (44.57)	184 (54.60)
1	28 (53.85)	24 (46.15)	52 (15.43)
2	9 (23.08)	30 (76.92)	39 (11.57)
3	9 (52.94)	8 (47.06)	17 (5.04)
4	11 (52.38)	10 (47.62)	21 (6.23)
5	3 (42.86)	4 (57.14)	7 (2.08)
6	4 (66.67)	2 (33.33)	6 (1.78)
7	0 (0.00)	3 (100.00)	3 (0.89)
8	0 (0.00)	2 (100.00)	2 (0.59)
9	1 (100.00)	0 (0.00)	1 (0.30)
10	0 (0.00)	1 (100.00)	1 (0.30)
11	0 (0.00)	1 (100.00)	1 (0.30)
13	0 (0.00)	1 (100.00)	1 (0.30)
14	1 (100.00)	0 (0.00)	1 (0.30)
15	1 (100.00)	0 (0.00)	1 (0.30)

duration, use of compression and centre in a negative binomial regression model. Centre will be treated as a random effect. We assumed that the 10 centres in the study were randomly chosen from a population of centres where inference has to be made. The negative binomial regression model has been chosen as opposed to the Poisson regression so that we can account for overdispersion (variance greater than the mean).

The adverse events were assessed by the nurse by categorising their relationship with treatments (Table 18). The majority of the adverse events (81% and 86% for NSAEs and SAEs, respectively) were categorised as unrelated to the treatment received. None of the NSAEs was classified as 'not able to assess if related', while only one SAE (1%) in the ultrasound group was classified as 'not able to assess if related'. There were two SAEs and one NSAE that were not categorised (missing data). Percentages are calculated on the adverse events that were categorised.

In the random effects negative binomial regression model, in which the response was the number of NSAEs per patient during the entire time of follow-up in the study, the explanatory variables in the model were the fixed effects [treatment, log(area), log(duration), ulcer compression] and the random effect (centre). The results show that there was a significant effect of treatment ($p=0.0411$). There was a non-significant effect of log(area) ($p=0.4247$), log(duration) ($p=0.2395$) and ulcer compression ($p=0.9882$). Therefore, the number of NSAEs was significantly associated with the treatment received, with more NSAEs episodes in the ultrasound group than in the standard care group. The number of NSAEs was not related to baseline ulcer area, baseline

TABLE 18 Relationship between adverse events (non-serious and serious) and the randomised treatment (nurses' assessment)

Relationship	NSAE			SAE		
	Standard care	Ultrasound	Total (%)	Standard care	Ultrasound	Total (%)
Unrelated	183	178	361 (81.31)	33	41	74 (86.05)
Unlikely to be related	11	46	57 (12.84)	2	7	9 (10.47)
Possibly related	0	17	17 (3.83)	0	0	0 (0.00)
Probably related	0	6	6 (1.35)	1	0	1 (1.16)
Definitely related	0	3	3 (0.68)	1	0	1 (1.16)
Not able to assess if related	0	0	0 (0.00)	0	1	1 (1.16)
Total	194	250	444	37	49	86

ulcer duration or baseline compression usage. The estimate of random centre effect SD was 1.39 (standard error 0.38, $p=0.0051$). Therefore, the correlation of patients within a centre could not be ignored. Owing to overdispersion in the data, an ordinary Poisson regression did not fit the data very well, but this random effects negative binomial model did. The dispersion parameter was estimated as 0.57 (standard error 0.13, $p=0.0016$), giving strong evidence of zero inflation (more patients with no NSAEs than those modelled under negative binomial regression model). A zero-inflated random effects negative binomial model was fitted, but results did not differ much from those above so the random effects negative binomial model without considering zero inflation was considered the best model here.

In the random effects negative binomial regression model in which the response was the number of SAEs per patient during the entire time of follow-up in the study, the explanatory variables in the model were the fixed effects [treatment, log(area), log(duration), ulcer compression] and the random effect (centre). The results show that there was a non-significant effect of treatment ($p=0.3904$) and ulcer compression ($p=0.6585$). There was a borderline effect of log(area) ($p=0.0781$) and log(duration) ($p=0.0647$). Therefore, there was no statistically significant difference in the number of SAEs due to treatment received or baseline record of compression used. There was relatively weak evidence that baseline ulcer area and baseline ulcer duration are associated with number of SAEs. The estimate of random centre effect SD was 0.51 (standard error 0.18, $p=0.0211$). Therefore, the correlation of patients within a centre could not be ignored. A zero-inflated random effects negative binomial model was fitted to the data but the results did not differ much from those above; hence, the random effects negative binomial model without considering zero inflation was considered the best model here (dispersion parameter 0.91, standard error 0.47, $p=0.0884$, giving weak evidence of zero inflation).

In the random effects negative binomial regression model in which the response was the number of NSAEs plus SAEs (adverse events) per patient during the entire time of follow-up in the study, the explanatory variables in the model were the fixed effects [treatment, log(area), log(duration), ulcer compression] and the random effect (centre). The results (Table 19) show that there was a significant effect of treatment ($p=0.0446$). There was a non-significant effect of log(area) ($p=0.1963$) and ulcer compression at baseline ($p=0.9882$). There was a borderline significant effect of log(duration) ($p=0.0843$). Therefore, the number of adverse events was significantly associated with the treatment received, with more adverse events episodes in the ultrasound group than in the standard care group. There was no statistically significant association between the number of adverse events and baseline ulcer area, or baseline compression usage, and a weak but significant association with baseline ulcer duration. The estimate of random centre effect SD was 1.18 (standard error 0.32, $p=0.0053$). Therefore, the correlation of patients within a centre

TABLE 19 Parameter estimate (standard error), *p*-values and 95% CI of the random effects negative binomial regression model fitted to the NSAE data, SAE data and number of SAEs and NSAEs combined

Parameter	NSAEs			SAEs			NSAEs and SAEs combined		
	Estimate (standard error)	<i>p</i> -value	95% CI	Estimate (standard error)	<i>p</i> -value	95% CI	Estimate (standard error)	<i>p</i> -value	95% CI
<i>Fixed effects</i>									
Intercept	-0.84 (0.55)	0.1599	-2.08 to 0.40	-2.55 (0.52)	0.0008	-3.72 to -1.37	-0.63 (0.47)	0.2157	-0.69 to 0.44
Treatment (ultrasound vs standard care)	0.35 (0.14)	0.0411	0.02 to 0.67	0.23 (0.25)	0.3904	-0.34 to 0.79	0.30 (0.13)	0.0446	0.01 to 0.60
Log(area)	0.05 (0.05)	0.4247	-0.08 to 0.17	0.19 (0.09)	0.0781	-0.03 to 0.40	0.07 (0.05)	0.1963	-0.04 to 0.18
Log(duration)	0.08 (0.06)	0.2395	-0.06 to 0.22	0.22 (0.10)	0.0647	-0.02 to 0.45	0.11 (0.06)	0.0843	-0.02 to 0.24
Ulcer compression (yes vs no)	-0.003 (0.21)	0.9882	-0.46 to 0.47	-0.16 (0.36)	0.6585	-0.98 to 0.65	-0.01 (0.19)	0.9481	-0.44 to 0.41
<i>Covariance parameters</i>									
Centre effect	1.39 (0.38)	0.0051	0.54 to 2.26	0.51 (0.18)	0.0211	0.10 to 0.93	1.18 (0.32)	0.0053	0.45 to 1.91
Dispersion parameter	0.57 (0.13)	0.0016	0.28 to 0.88	0.91 (0.47)	0.0884	-0.17 to 1.98	0.49 (0.11)	0.0015	0.25 to 0.74

could not be ignored. A zero-inflated random effects negative binomial model was fitted, but results did not differ much from those above, so the random effects negative binomial model without considering zero inflation was considered the best model here (dispersion parameter 0.49, standard error: 0.11, $p = 0.0015$), giving strong evidence of zero inflation.

Summary

There was no evidence of a statistically significant effect of therapeutic ultrasound on the healing of hard-to-heal venous leg ulcers when compared with standard care alone. There was a significant centre effect observed in the trial, such that rates of ulcer healing differed significantly between centres.

Patients with smaller ulcers at baseline, those receiving high compression at baseline and those with shorter duration ulcers at baseline all healed more quickly than those with larger or older ulcers or ulcers in people that were not receiving high compression at baseline, after adjusting for all other factors.

There was no evidence of a statistical significant effect of low-dose ultrasound on QoL (as measured by SF-12) etc.; however, patients with older ulcers at baseline reported significantly poorer QoL as measured by the PCS and MCS component scores of the SF-12. Significantly more people receiving therapeutic ultrasound experienced adverse events than those receiving standard care; most adverse events were non-serious.

Chapter 5

Economic analysis

Three hundred and thirty-seven participants were recruited to VenUS III. There were 169 participants allocated to standard care and 168 to ultrasound plus standard care.

Outcomes of the economic analysis

Resource use and cost

Ultrasound plus standard care

Over the 12 weeks of ultrasound treatment, participants in the treatment arm had an average of 15.35 nurse consultations and 10.25 applications of ultrasound (the trial protocol suggested no more than one ultrasound application per week). Each ultrasound application lasted, on average, 7.21 minutes. Patients received therapeutic ultrasound in 77% of consultations. The details can be found in *Table 20*.

Compression therapy

Table 21 presents the total number of times high compression was applied in both arms over the period of trial: at 84% of nurse consultations in the standard care arm and 78% of nurse consultations in the ultrasound arm.

TABLE 20 Nurse-recorded treatments in the ultrasound arm (for the first 12 weeks)

Treatment recorded	Ultrasound (<i>n</i> =168)
Number of nurse consultations, per patient	
Mean (SD)	15.35 (8.88)
Median (min, max)	13 (2, 51)
Missing	9
Number of ultrasound applications, per patient	
Mean (SD)	10.25 (2.96)
Median (min, max)	11 (1, 15)
Missing	9
Duration of ultrasound application (minutes), per patient	
Mean (SD)	7.21 (2.32)
Median (min, max)	7 (1, 10)
Missing	9
Proportion of visits receiving ultrasound, per patient	
Mean % (SD)	77 (24)
Median % (min, max)	86 (14, 100)
Missing	9

max, maximum; min, minimum.

Health-care consultations

The number of consultations recorded by nurses for the full follow-up period is shown in *Table 22*; standard care patients received, on average, 41.34 nurse consultations compared with 44.90 in the ultrasound arm. Most nurse consultations took place in the leg ulcer clinic or patients' homes (75% and 76% for standard care and ultrasound arms, respectively). Note that we received no information regarding treatments received for 18 patients (10 in the standard care arm and 8 in the ultrasound arm) and they were, therefore, recorded as missing throughout the economic analysis. There was also one participant in the ultrasound arm for whom no information about the duration of ultrasound treatments was available.

Total costs

The total cost for each participant was calculated by summing the cost of compression therapy, cost of health-care consultation and the cost of ultrasound machine where applicable. The cost of health-care consultation was the main contributor to the total cost. Quarterly and annual (unadjusted) figures are presented in *Table 23*.

TABLE 21 The use of compression therapy

Compression therapy	% (N)	
	Ultrasound (n= 168)	Standard care (n= 169)
Compression bandages applied		
Four-layer high compression	30.67 (2151)	34.62 (2241)
Three-layer high compression	18.89 (1325)	23.84 (1543)
Two-layer high compression	15.16 (1063)	13.24 (857)
Short-stretch	13.13 (921)	12.44 (805)
Three-layer reduced compression	12.09 (848)	10.32 (668)
Low compression	3.56 (250)	2.15 (139)
No compression	6.49 (455)	3.4 (220)
Knitted viscose dressing applied		
Yes	44.82 (3070)	39.98 (2556)
No	55.18 (3779)	60.14 (3856)

TABLE 22 Nurse-recorded treatments in both arms (1 year)

Nurse therapy	Ultrasound (n= 168)	Standard care (n= 169)
Number of nurse consultations, per patient		
Mean (SD)	44.90 (43.16)	41.34 (46.76)
Median (min, max)	30 (2, 307)	28 (1, 354)
Missing (%)	8 (4.8)	10 (5.9)
Location of consultations, n (%)^a		
Home	2534 (35.58)	2344 (36.02)
Leg ulcer clinic	2883 (40.48)	2545 (39.11)
GP surgery	1107 (15.54)	1071 (16.46)
Other	548 (7.69)	534 (8.21)
Nursing home	49 (0.69)	13 (0.20)
Leg ulcer club	1 (0.01)	1 (0.02)

max, maximum; min, minimum.

a Full number of visits in the study sample.

Table 24 shows the adjusted annual cost for each arm and their mean difference. To account for the censored nature of the data, possible baseline imbalances and stratification variables, the inverse probability-weighted multiple regression was used. This allows estimation of the mean cost difference between the two arms adjusting for covariates: baseline ulcer duration (logarithmic), ulcer area (logarithmic), use or not of compression therapy and centres (aggregating centres with fewer than five cases). The results of the base-case analysis show that adding ultrasound treatment to standard care costs, on average, £197.88 more per participant per year (95% bias-corrected CI –£35.19 to £420.32). This difference was not statistically significant.

Health benefits

Time to healing

The estimated mean time to healing (over 12 months) was 245.0 days for standard care and 259.7 days for ultrasound plus standard care (Table 25). The result was in favour of the control

TABLE 23 Total and quarterly unadjusted costs (base-case analysis)

Time point	Ultrasound (n=168)	Standard care (n=169)
Months 1–3		
Mean (SD)	572.8 (538.6)	456.7 (538.9)
Median (min, max)	355.5 (64.6, 4544.9)	272.8 (20.6, 4413.9)
Missing (%)	8 (4.8)	10 (5.9)
Months 4–6		
Mean (SD)	436.5 (580.8)	343.4 (605.5)
Median (min, max)	271.1 (0.0, 4681.3)	207.7 (0.0, 4258.5)
Missing (%)	25 (14.3)	24 (14.2)
Months 7–9		
Mean (SD)	333.8 (555.5)	291.9 (547.9)
Median (min, max)	182.8 (0.0, 4524.3)	142.8 (0.0, 3785.3)
Missing (%)	35 (20.2)	34 (20.1)
Months 10–12		
Mean (SD)	290.2 (570.3)	283.2 (607.6)
Median (min, max)	63.9 (0.0, 4985.4)	31.1 (0.0, 4431.5)
Missing (%)	45 (26.2)	46 (27.2)
Total costs		
Mean (SD)	1471.0 (1884.7)	1237.4 (2055.7)
Median (min, max)	902.0 (135.6, 16,288.6)	670.3 (20.61, 16,889.3)
Missing (%)	8 (4.8)	10 (5.9)

max, maximum; min, minimum.

TABLE 24 Adjusted^a annual costs (base-case analysis)

Arm	Mean cost (£)	95% bias-corrected CI (£)
Ultrasound	1583.39	1427.51 to 1728.70
Standard care	1385.51	1223.84 to 1549.21
Difference ^b	197.88	–35.19 to 420.32

a Adjusted for baseline ulcer duration (logarithmic), ulcer area (logarithmic), use or not of compression therapy and centres (aggregating centres with fewer than five cases).

b Difference = ultrasound with standard care – standard care alone.

arm (standard care alone). However, the difference (14.7 days) was not statistically significant (95% bias-corrected CI –32.7 to 56.8 days). The estimation was based on the IPW regression with covariates of baseline ulcer duration (logarithmic), ulcer area (logarithmic), use or not of compression therapy and centres (aggregating centres with fewer than five cases).

Utility and quality-adjusted life-years

The unadjusted utility (EQ-5D) scores are shown in *Table 26*. The average utility scores at baseline for control and treatment arms were 0.537 and 0.509, respectively, indicating some imbalance. Based on individuals' utility scores, the total QALY was calculated and the results are shown in *Table 27*. The mean annual unadjusted QALY for the standard care arm was 0.568 and for ultrasound was 0.550 (*Table 28*).

TABLE 25 Adjusted^a mean time to healing

Arm	Mean (days)	95% bias-corrected CI (days)
Ultrasound	259.7	232.7 to 302.5
Standard care	245.0	230.6 to 282.3
Difference ^b	14.7	–32.7 to 56.8

a Adjusted for baseline ulcer duration (logarithmic), ulcer area (logarithmic), use or not of compression therapy and centres (aggregating centres with fewer than five cases).

b Difference = ultrasound with standard care – standard care alone.

TABLE 26 Unadjusted utility scores (EQ-5D index scores)

Time point	Ultrasound (<i>n</i> = 168)	Standard care (<i>n</i> = 169)
Baseline		
Mean (SD)	0.509 (0.340)	0.537 (0.322)
Median (min, max)	0.620 (–0.349, 1.000)	0.620 (–0.484, 1.000)
Missing (%)	19 (11)	12 (7)
3 months		
Mean (SD)	0.472 (0.365)	0.527 (0.342)
Median (min, max)	0.587 (–0.426, 1.000)	0.62 (–0.239, 1.000)
Missing (%)	34 (20)	34 (20)
6 months		
Mean (SD)	0.497 (0.362)	0.55 (0.335)
Median (min, max)	0.587 (–0.594, 1.000)	0.62 (–0.239, 1.000)
Missing (%)	44 (26)	34 (20)
9 months		
Mean (SD)	0.497 (0.373)	0.546 (0.346)
Median (min, max)	0.620 (–0.429, 1.000)	0.620 (–0.181, 1.000)
Missing (%)	55 (33)	53 (31)
12 months		
Mean (SD)	0.534 (0.359)	0.544 (0.36)
Median (min, max)	0.620 (–0.594, 1.000)	0.620 (–0.181, 1.000)
Missing (%)	47 (28)	60 (36)

max, maximum; min, minimum.

TABLE 27 Quarterly and annual unadjusted QALYs

Time point	Ultrasound (n=168)	Standard care (n=169)
1–3 months		
Mean (SD)	0.126 (0.079)	0.133 (0.074)
Median (min, max)	0.147 (–0.087, 0.250)	0.151 (–0.025, 0.250)
Missing (%)	47 (28)	43 (25)
4–6 months		
Mean (SD)	0.124 (0.083)	0.134 (0.078)
Median (min, max)	0.138 (–0.104, 0.250)	0.151 (–0.052, 0.250)
Missing (%)	54 (32)	48 (28)
7–9 months		
Mean (SD)	0.130 (0.083)	0.137 (0.082)
Median (min, max)	0.155 (–0.118, 0.250)	0.155 (–0.052, 0.250)
Missing (%)	67 (40)	58 (34)
10–12 months		
Mean (SD)	0.136 (0.082)	0.141 (0.081)
Median (min, max)	0.155 (–0.118, 0.250)	0.155 (–0.045, 0.250)
Missing (%)	67 (40)	73 (43)
Annual (complete cases only)		
Mean (SD)	0.550 (0.301)	0.568 (0.287)
Median (min, max)	0.625 (–0.342, 1.000)	0.629 (–0.160, 1.000)
Missing (%)	89 (53)	88 (52)

max, maximum; min, minimum.

TABLE 28 Adjusted^a annual QALYs

Arm	Mean QALYs (years)	95% bias-corrected CI (years)
Ultrasound	0.515	0.488 to 0.537
Standard care	0.525	0.499 to 0.545
Difference ^b	–0.009	–0.042 to 0.024

a Adjusted for baseline utility, ulcer duration (logarithmic), ulcer area (logarithmic), use or not of compression therapy and centres (aggregating centres with fewer than five cases).

b Difference = ultrasound with standard care – standard care alone.

After adjusting for the censored nature of data, imbalance of utility score at baseline and other covariates, the mean QALY was 0.525 for standard care and 0.515 for ultrasound. The difference (–0.009 QALYs) was not statistically significant (95% bias-corrected CI –0.042 to 0.024 QALYs).

Cost-effectiveness and uncertainty

The base-case analysis shows that ultrasound with standard care is expected to be more costly and less beneficial (as measured by both QALY and time to healing) than standard care alone. As summarised in *Table 29*, compared with standard care alone, individuals who received ultrasound plus standard care took an average of 14.7 days longer to heal, had 0.009 fewer QALYs and higher treatment costs (by £197.88). Ultrasound therapy plus standard care for leg ulcers was therefore dominated by standard care alone and should not be adopted. However, none of the

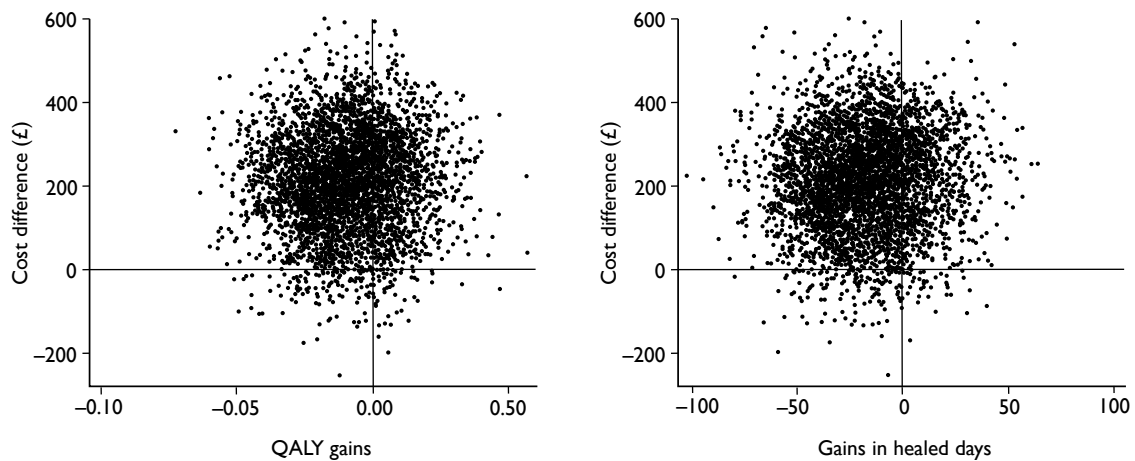


FIGURE 7 Cost-effectiveness plane.

TABLE 29 Summary table for incremental differences

Variables	Mean annual costs (95% CI ^a)	QALYs (95% CI ^a)	Time to healing (95% CI ^a)	Gain in ulcer-free day ^c (95% CI ^a)	ICER (cost per QALY/cost per ulcer-free day)
Ultrasound	1583.39	0.515	259.7	–	Dominated
Standard care	1385.51	0.525	245.0	–	–
Difference ^b	197.88 (–35.19 to 420.32)	–0.009 (–0.042 to 0.024)	14.7 (–32.7 to 56.8)	–14.7 (–56.8 to 32.7)	–

a Based on the bias-corrected bootstrap CI.

b Difference = ultrasound with standard care – standard care alone.

c Gain in ulcer-free day is the same as the difference in mean time to healing between arms but with the opposite sign.

differences in costs and benefits between these alternative treatments were statistically significant, indicating uncertainty which should be examined using bootstrapping.

The incremental cost-effectiveness plane, shown in *Figure 7*, was drawn to demonstrate the uncertainty associated with the mean difference in cost and health benefits between two trial arms, by plotting the non-parametric bootstrapping results – 4000 replicates of difference in costs and health benefits (QALYs and ulcer-free days). As shown in *Figure 7*, in the cost–utility (cost per additional QALY) analysis, the majority of points (67%) fall into the north-west quadrant, indicating that ultrasound with standard care is dominated by standard care alone. The cost-effectiveness analysis (i.e. cost per additional ulcer-free day) similarly indicates standard care to be dominant, with 74% of the estimates falling in the north-west quadrant.

Figure 8 presents the CEACs. For the cost per QALY analysis, according to the figure, the probability of ultrasound treatment being cost-effective is < 20% given the willingness to pay for additional QALY up to £30,000. Therefore, based on the current trial evidence, it is unlikely that ultrasound with standard care is cost-effective. Similarly, in the cost per ulcer-free day analysis, the probability of ultrasound treatment being cost-effective is around 20% maximum for any willingness to pay for an additional ulcer-free day.

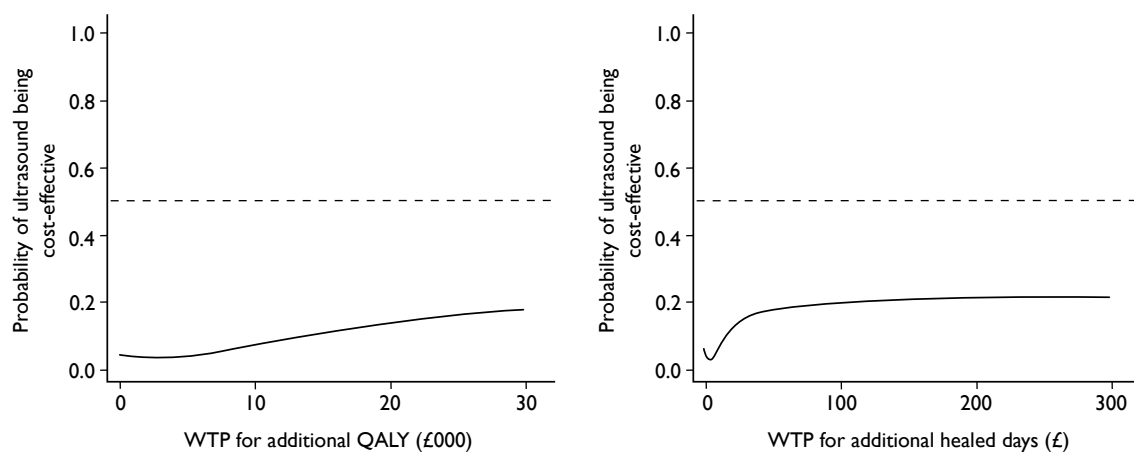


FIGURE 8 Cost-effectiveness acceptability curve (base-case analysis). WTP, willingness to pay.

Sensitivity analysis

Scenario 1

Sensitivity analysis was conducted to investigate the impact on the cost-effectiveness results of using patient-reported data regarding the health-care consultations. Ulcer-related doctor, nurse and hospital outpatient visits were extracted from postal questionnaires received from patients every 3 months during the follow-up period.

The number of ulcer-related doctor/nurse/hospital outpatient visits is shown in *Table 30*. Patients reported far fewer health-care consultations than the nurses (see *Table 22*). On average, patients reported a total of 25 nurse consultations in the standard care arm and 37 consultations in the ultrasound arm whereas the nurses reported 41 (standard care) and 45 (ultrasound) consultations.

The unadjusted costs for each arm based on patient-reported data are shown in *Table 31*. The adjusted mean costs for the standard care arm were £1650.50 per participant per year (95% bias-corrected CI £1439.20 to £1888.30) and £1790.70 for the ultrasound arm (95% bias-corrected CI £1553.60 to £2018.40). The difference in means between two arms was £140.20 and was not significant (95% bias-corrected CI -£186.60 to £438.20). The estimated difference in this scenario was lower than that in the base case.

As only the cost of ultrasound was subjected to sensitivity analysis, the health benefit estimate is equivalent to base case. Similar to the results observed in the base-case analysis, in this scenario ultrasound with standard care is expected to be dominated by standard care alone (as shown in *Figure 9*) and ultrasound with standard care treatment is unlikely to be cost-effective based on the current trial evidence (as shown in *Figure 10*).

Scenario 2

One-way sensitivity analysis was conducted to investigate the influence of the equipment cost of ultrasound machines on the adjusted cost difference, shown in *Figure 11*. With a decrease (from 88.05 to 0.00 with every 10% decrease) in the equipment cost of ultrasound machine, the adjusted cost difference between two arms also decreased. The adjusted cost difference dropped from £197.88 with the full equipment cost as used in the base-case analysis to £110.60 with no equipment cost involved. The remaining difference was mostly caused by the incurred cost of extra nurse time in applying ultrasound treatments. However, none of these estimates on cost difference was statistically significant. Thus, the uncertainty around the cost difference remained.

TABLE 30 Number of ulcer-related consultations (visits) reported by patients

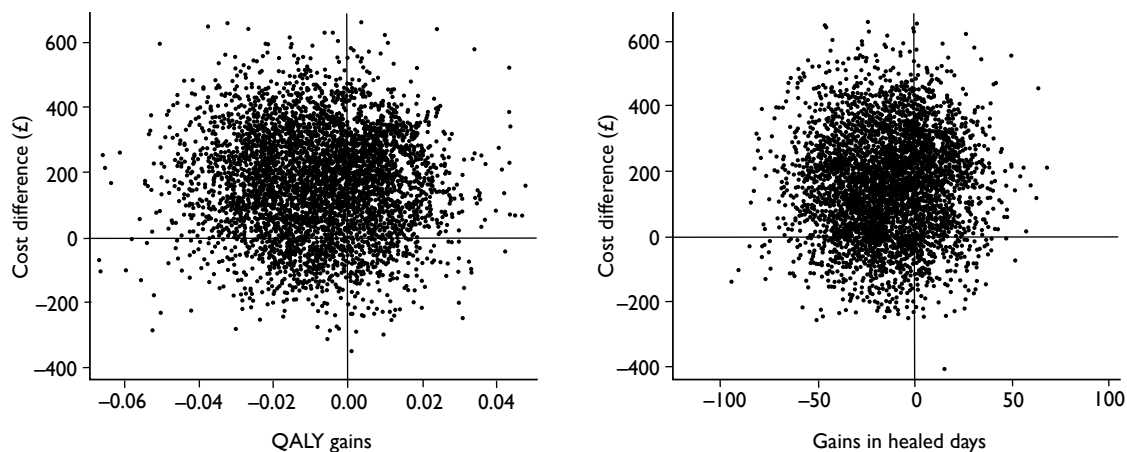
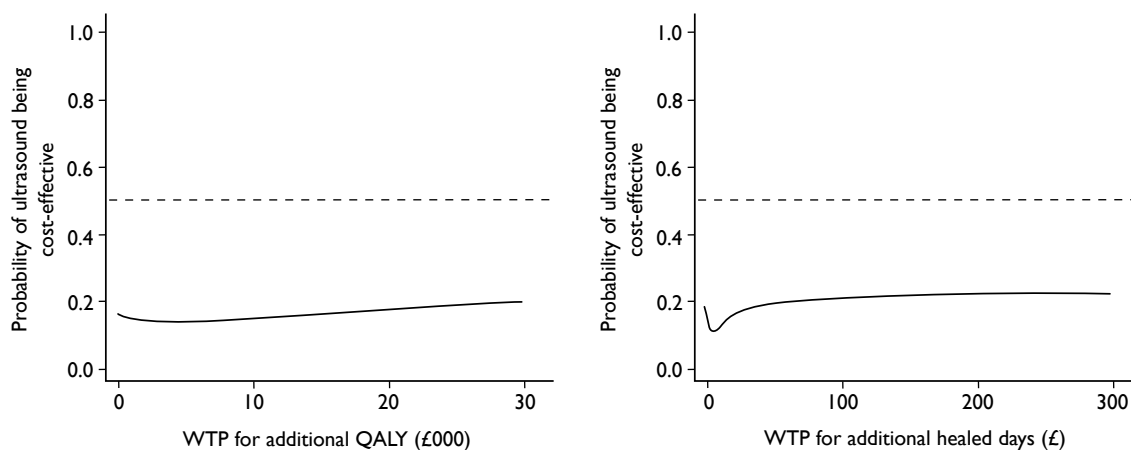
Time	Event		Ultrasound (n= 168)	Standard care (n= 169)
3 months	Doctor visits related to ulcers	Mean (SD)	0.8 (2.7)	0.6 (2.2)
		Median (min, max)	0 (0, 24)	0 (0, 15)
		Missing	41 (25.0)	41 (24.3)
	Nurse visits related to ulcers	Mean (SD)	11.1 (16.3)	8.9 (12.0)
		Median (min, max)	3 (0, 84)	0 (0, 57)
		Missing	39 (23.8)	55 (32.5)
	Hospital visits related to ulcer	Mean (SD)	3.7 (6.9)	3.4 (7.0)
		Median (min, max)	0 (0, 36)	0 (0, 36)
		Missing	27 (16.7)	31 (18.3)
6 months	Doctor visits related to ulcers	Mean (SD)	0.7 (2.5)	0.7 (2.3)
		Median (min, max)	0 (0, 15)	0 (0, 15)
		Missing	57 (34.5)	49 (29.0)
	Nurse visits related to ulcers	Mean (SD)	9.9 (15.5)	8.8 (14.2)
		Median (min, max)	0 (0, 84)	0 (0, 84)
		Missing	56 (33.9)	52 (30.8)
	Hospital visits related to ulcers	Mean (SD)	2.9 (8.3)	2 (6.4)
		Median (min, max)	0 (0, 66)	0 (0, 60)
		Missing	43 (26.2)	34 (20.1)
9 months	Doctor visits related to ulcers	Mean (SD)	1 (3.3)	0.8 (2.2)
		Median (min, max)	0 (0, 21)	0 (0, 12)
		Missing	58 (35.1)	68 (40.2)
	Nurse visits related to ulcers	Mean (SD)	8.4 (15.4)	8.6 (15.3)
		Median (min, max)	0 (0, 84)	0 (0, 84)
		Missing	59 (35.7)	67 (39.6)
	Hospital visits related to ulcers	Mean (SD)	2 (5.8)	2.1 (5.4)
		Median (min, max)	0 (0, 48)	0 (0, 30)
		Missing	51 (31.0)	52 (30.8)
12 months	Doctor visits related to ulcers	Mean (SD)	1 (3.5)	1.4 (5.9)
		Median (min, max)	0 (0, 30)	0 (0, 45)
		Missing	55 (33.3)	67 (39.6)
	Nurse visits related to ulcers	Mean (SD)	8.1 (14.0)	5.9 (13.9)
		Median (min, max)	0 (0, 84)	0 (0, 84)
		Missing	60 (36.3)	72 (42.6)
	Hospital visits related to ulcers	Mean (SD)	1.4 (4.9)	1.7 (5.2)
		Median (min, max)	0 (0, 36)	0 (0, 36)
		Missing	43 (26.2)	56 (33.1)
Total (completed cases only)	Doctor visits related to ulcers	Mean (SD)	2.91 (6.74)	2.32 (7.60)
		Median (min, max)	0 (0, 36)	0 (0, 96)
		Missing	98 (58.3)	94 (55.6)
	Nurse visits related to ulcers	Mean (SD)	36.73 (50.56)	25.32 (35.29)
		Median (min, max)	15 (0, 294)	12 (0, 153)
		Missing	94 (56.0)	103 (60.9)
	Hospital visits related to ulcers	Mean (SD)	8.26 (16.82)	8.84 (19.01)
		Median (min, max)	0 (0, 90)	0 (0, 96)
		Missing	71 (42.3)	76 (45.0)

max, maximum; min, minimum.

TABLE 31 Unadjusted annual costs for each arm

Total costs (£)	Ultrasound (n=168)	Standard care (n=169)
Mean (SD)	1756.1 (2272.7)	1478.9 (2023.7)
Median (min, max)	906.7 (107.8, 14,882.9)	698.3 (0.0, 12,252.7)
Missing (%)	9 (4.8)	10 (5.9)

max, maximum; min, minimum.

**FIGURE 9** Cost-effectiveness plane (sensitivity analysis).**FIGURE 10** Cost-effectiveness acceptance curve (sensitivity analysis). WTP, willingness to pay.

The results here were based on 4000 bootstrap replicates and bias-corrected 95% CIs were reported.

Summary

Evidence from VenUS III suggests that low-dose ultrasound plus standard care is expected to be more costly and slightly less beneficial than standard care alone for the treatment of hard-to-heal venous leg ulcers. The analysis of uncertainty also shows that it is unlikely that this treatment strategy is cost-effective.

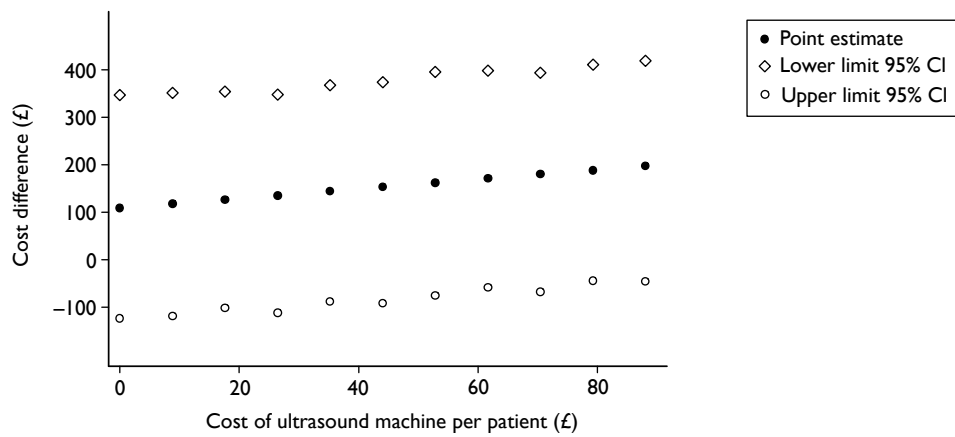


FIGURE 11 One-way sensitivity analysis result (bias-corrected 95% CI based on 4000 bootstrap replicates).

Based on these data, low-dose ultrasound is deemed not to be cost-effective and thus should not be recommended for adoption in the NHS. The results remained unchanged when the patient-reported health-care consultation data were used.

Decreasing the equipment cost of ultrasound machine did not affect the overall conclusion.

Chapter 6

Ultrasound output verification test and servicing

A total of 40 therapeutic ultrasound machines (EMS Therasonic 355 Physiotherapy systems) were purchased for use in VenUS III. Given that previous studies have indicated that there can be differences between the 'nominal' dose and that which is actually delivered by the machines,⁴² the study team wanted to ensure that the machines were functioning accurately. Since some of these differences can be apparent at machine delivery and some are due to drift or step changes in output,⁴³ two forms of testing were deemed necessary.

Firstly, prior to the commencement of the study, all machines were tested by the NPL in order to ascertain whether they were delivering ultrasound at the necessary frequency and intensity.

Secondly, the ultrasound machines were serviced by the manufacturer 3 months after the site had recruited its first patient allocated to ultrasound and 3-monthly thereafter.

Initial testing by the National Physical Laboratory

The NPL was asked to conduct acceptance testing of the machines (including retesting of any that fail initially), which was to include:

- measurement of total acoustic power at 0.5 W/cm^2 on continuous wave mode and also on a specified pulsed wave setting, using NPL absorbing target radiation force balance
- measurement of effective radiating area (A_{ER}) at 1 MHz, using absorbing apertures for the majority of machines
- pass/fail criteria consistent with the current versions of International Electrotechnical Commission (IEC) 60601-2-5 and IEC 61689.

In order for a machine to pass, any deviation from nominal had to be 20% or less for all of the tests conducted. The methods used by the NPL to obtain the necessary measurements can be found in *Appendix 10*.

The machines were initially sent for testing in two batches following consecutive delivery from the suppliers. The first batch contained two machines and the second batch consisted of the remaining 38 machines.

Results of the acceptance testing

The number of machines acceptance tested and passed is shown in *Table 32*.

TABLE 32 Machine acceptance testing data

Acceptance test	Number tested	Number failed	NPL test report reference	Results ^a shown in
Initial testing	40	11	U2263 and U2310	<i>Appendix 10</i>
Retesting	11	1	U2419	<i>Appendix 10</i>
Second retesting	1	1	U2617	<i>Appendix 10</i>

a Machines that failed are indicated by a cross with the failed test result circled.

Auditing ultrasound machine performance

The ultrasound machines were assessed to check the intensity of ultrasound delivered throughout the study (see *Appendix 10*). This originally was conducted by the ultrasound machine suppliers at each clinical site except for those sites in regions where there was no engineer (Northern Ireland and Scotland). Each ultrasound machine was numbered so that patients who received treatment from individual machines could be identified. This check was first carried out 3 months after a site randomised its first ultrasound patient and 3-monthly thereafter.

Thirteen of the machines developed a problem at some time during the study, the most common being a discrepancy with the output requiring repair or adjustment, followed by transducer heads failing to operate (immediately obvious) owing to the pins in the connecting lead being bent as a result of incorrect/forceful insertion into machine.

The digital screen of one machine was broken and required replacing, while one further machine was stolen.

Chapter 7

Discussion

Here we report the largest trial ever undertaken of therapeutic ultrasound for wound treatment.^{76–78}

This trial is also much larger than any trial of ultrasound for fractures included in a recent systematic review⁷⁹ and was conducted and reported in accordance with international guidelines for research excellence.^{80,81}

We were stimulated to conduct this trial by summaries of the pre-existing trial evidence for the effects of ultrasound in wound healing generally⁷⁸ and leg ulcers specifically.⁷⁶ The evidence suggested that this trial was conducted following systematic reviews which identified a potential benefit of ultrasound therapy for venous ulcer healing; however, a definitive trial was needed because previous trials were small and had methodological weaknesses and/or incomplete reporting; hence, the results of the reviews were not conclusive and at high risk of bias. Furthermore, the clinical contexts in which the previous trials had taken place (e.g. before the widespread introduction of high-compression therapy) meant that their relevance to today's leg ulcer patients was dubious. The largest previous trial was undertaken prior to the introduction of high-compression therapy and, hence, ultrasound was used against a background of lower healing rates. We now know from prognostic studies and trials research that have established that high-compression therapy such as four-layer bandages heals the vast majority (80%) of venous ulcers within 12 months, and that ulcers which are $< 5 \text{ cm}^2$ and of < 6 months' duration are more likely to heal quickly.⁸ In designing this trial we therefore felt that adding an adjuvant therapy such as ultrasound to the treatment of small or new ulcers was unlikely. There is likely to be little benefit to adding an adjuvant therapy to the treatment of venous ulcers that are small or new. The sample size of a trial to find a benefit of adding ultrasound to the treatment of most venous ulcers would be very large given the high healing rate. This study, therefore, evaluated the addition of low-dose ultrasound to modern compression techniques for 'hard-to-heal' ulcers. We evaluated the effect of 12 weeks of low-dose ultrasound, delivered during the regular nurse visits consultations, on time to healing, cost-effectiveness of this treatment and adverse effects. The discussion summarises the key findings, considers possible mechanisms, compares these results with published studies, considers the limitations of the present study and, finally, summarises the clinical and research implications of the work.

Key findings

We compared the effects of low-dose ultrasound delivered alongside standard care with standard care alone on the time to healing of the reference (largest) ulcer. We found no evidence that adding low-dose ultrasound treatment to the standard package of care (low-adherent dressings and high-compression therapy) reduced the time to leg ulcer healing compared with standard care alone (log-rank statistic 0.25, $p = 0.61$). The final statistical model, which included a frailty component that accounted for a centre effect and the difference in healing rates between centres, and adjusted for baseline ulcer area, duration and the use of compression, resulted in a hazard ratio for healing (with ultrasound vs standard care alone) of 0.99 (95% CI 0.70 to 1.40, $p = 0.969$).

A small, statistically not significant difference in the median time to complete healing of all ulcers was observed. Median time to healing of the standard care group was 328 days, (95% CI 235 days, inestimable) compared with the median time to healing of the ultrasound group (median 365 days, 95% CI 224 days, inestimable). Wound triallists traditionally report healing outcomes in a plethora of different ways,⁷⁸ and there was no evidence of a difference between low-dose ultrasound and standard care for any measure of healing in this trial.

There was no difference between low-dose ultrasound plus standard care and standard care alone in the proportion of patients with ulcers healed at 12 months (72/168 in ultrasound vs 78/169 standard care), nor in the change in ulcer size at 4 weeks.

We did, however, confirm our earlier findings^{7,44} that baseline ulcer area and ulcer duration were statistically significant predictors of time to healing ($p < 0.0001$), with larger ulcers and those of longer duration taking longer to heal.^{7,61}

There was no evidence of a difference in recurrence of healed ulcers and few people had a recurrence within trial follow-up.

We investigated changes in HRQoL from baseline using the SF-12v2.⁴⁰

Our results confirm the previous findings that leg ulcer patients have a poorer physical health (PCS) than age norms. There was little change in the PCS score during the trial in both groups. There was no evidence of a statistically significant change in mental health scores (MCS) over time. We cannot conclude that ultrasound has any impact on HRQoL. As the SF-12 is a generic tool it is possible that it may have missed changes in ulcer-specific dimensions; however, previous work has demonstrated that the SF-12 and EQ-5D are sensitive to, and thus able to measure, change in venous leg ulcer patients.⁴⁷

There were more adverse events in the ultrasound group than in the standard care group. Given that this trial was open, and ultrasound is not currently used in practice, then it is possible that nurses were more likely to attribute adverse events (such as ulcer deterioration) to a treatment with which they are relatively unfamiliar. The overall adverse event rate (the number of people reporting any SAE or NSAE) was similar to that in VenUS I,⁷ in which the adverse event rate was approximately 40%.

We evaluated whether adding ultrasound to standard care was a cost-effective strategy for the management of venous leg ulceration in relation to standard care alone. The intervention requires an increase in treatment time and, hence, costs associated with nursing time. In addition, there is the need to purchase ultrasound machines. We found that ultrasound therapy as an adjuvant to standard care was found not a cost-effective treatment when compared with standard care alone. In the base-case analysis, while mean QALYs were very similar between groups, the mean cost of ultrasound was £197.88 (bias-corrected 95% CI –£35.19 to £420.32) *higher* than the mean cost of standard care per participant per year. The analysis of uncertainty surrounding these estimates shows that it is unlikely that this treatment strategy is cost-effective, while health benefits were lower.

Sensitivity analyses were conducted for the cost-effectiveness. These assessed the impact of altering various assumptions such as nurse-reported rather than patient-reported data on consultation rates and reducing the costs of the ultrasound treatment (lower cost machine or used more widely). Neither approach had any impact on the findings.

Consideration of possible explanations

There are two explanations of our findings: that there is a treatment effect but this trial failed to detect it (either by chance or due to methodological problems) or ultrasound at this dose and frequency does not accelerate healing of venous ulcers of long duration/large area. We minimised the play of chance accounting for the lack of an effect by having a large sample size. We minimised detection bias by using confirmed healing date by photographic assessment. The possibility that ultrasound machines did not deliver the prescribed dose was reduced by having them serviced and calibrated regularly, and we recorded all treatments given to ascertain if there was evidence of performance bias (e.g. extra treatments in the standard care group), which there was not. The decision to use this form of ultrasound was based upon the previous evidence (the largest trial) and the need to balance the need to deliver leg ulcer care in an efficient manner, with weekly visits to renew dressings and bandages, and the desire to deliver ultrasound more frequently. We stopped delivering ultrasound at 12 weeks as we felt this was a pragmatic approach to evaluating the addition of a novel therapy that took account of the extra treatment time required by the nurse. We felt that asking nurses to apply ultrasound for the whole trial period would have resulted in disillusionment if nurses felt that there was no discernible benefit, as this would increase the workload significantly: this would have hampered recruitment. The lack of any treatment effect difference, as seen in the Kaplan–Meier curves, seems consistent with there being no effect on healing rate within the first 12 weeks.

Comparison with other studies/reviews

The explanation for the difference between our results and those of previous trials probably lies in the much lower risk of bias in our study and our larger sample size, ensuring that chance differences were less likely to manifest as type 1 errors. We designed this trial in 2003, at which time there were seven trials summarised in a systematic review,³² two of which were not randomised.^{26,27} Of the remaining five randomised controlled trials (RCTs), three reported healing data for a 12-week time point, all of which were at medium or high risk of bias.^{25,29,30} Individually these all identified a benefit associated with ultrasound for the outcome of proportion of ulcers healed at 12 weeks, though none of the differences was statistically significant when analysed by the numbers randomised rather than by complete case analysis. When the three trials were pooled, however (heterogeneity was minimal with an $I^2=0$), a statistically significant benefit associated with ultrasound, over sham or standard care, was apparent (relative risk 1.5, 95% CI 1.0 to 2.3, $p=0.047$) (*Figure 12*).

We can now add the VenUS III data into this meta-analysis, by taking the numbers healed at 12 weeks (*Figure 13*, fixed effect model, $I^2=0$). Overall, although more people healed with ultrasound than with sham ultrasound or standard care, this difference was not statistically significant ($p=0.095$). Furthermore, since VenUS III is the only trial which met all the validity criteria of adequate randomisation, full allocation concealment, blinded outcome assessment and intention to treat analysis, we would argue that the VenUS III result is the most valid. The conclusion we would therefore draw from all the evidence is that low-dose therapeutic ultrasound does not confer any benefit on the healing of hard-to-heal venous leg ulcers.

Strengths and limitations of the study

We did recruit people who had hard-to-heal ulcers and, therefore, in whom clinicians might consider adding additional interventions, above standard care packages of dressing and bandages,

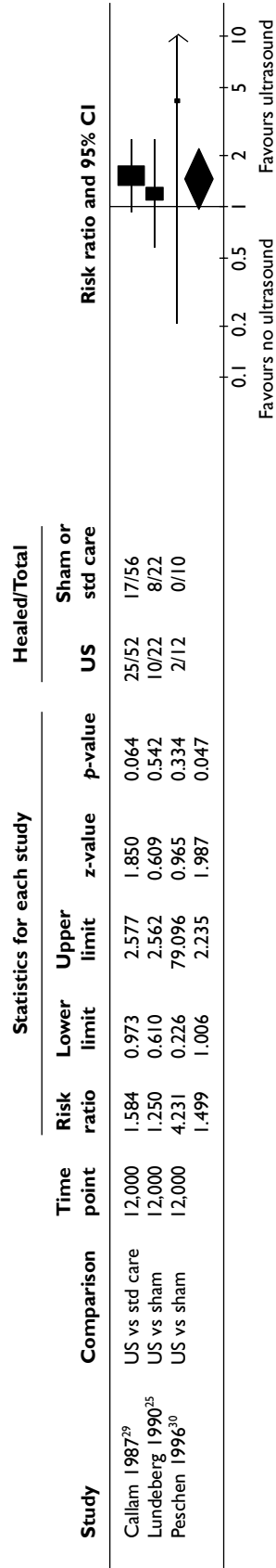


FIGURE 12 Plot of meta-analysis for venous ulcers trials before Venous Ulcer Study III (numbers healed at 12 weeks). Std, standard; US, ultrasound.

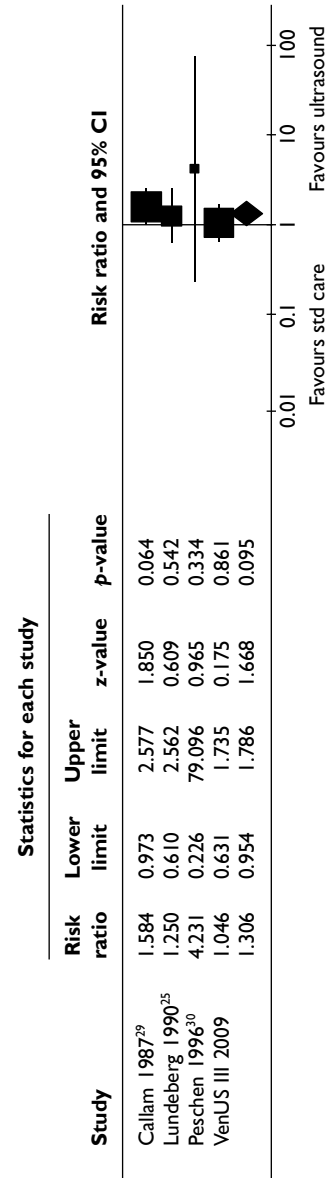


FIGURE 13 Plot of meta-analysis for venous ulcers healing with ultrasound after VenUS III (numbers healed at 12 weeks).

to aid healing. Ulcers in the people recruited were, on the whole, large (12 cm²) and chronic (1 year duration). The people recruited were representative of the venous ulcer population in terms of age and gender.¹

We had originally estimated that we would recruit 336 people from six sites in 18 months. It took twice this time and 12 centres to meet our recruitment target. This allowed us to detect a 7-week difference in time to healing (with 80% power, 5% alpha). Our finding of no evidence of difference is not likely to be due to lack of power (type 2 error).

In common with most trials of wound care in the community, we were not able to arrange simultaneous, blinded outcome assessment by an independent assessor (blinded to the use of ultrasound or not) owing to logistics and costs. Like VenUS II, we used remote, blinded assessment of serial photographs and confirmed the agreement between two clinical nurses in making this judgement, and in agreement with the local clinical nurse.

Our experience of using cameras for outcome assessment, akin to VenUS II, to obtain blinded outcome assessments was not without challenge. In some cases, we did not receive photographs (e.g. where a camera was stolen or camera data cards lost) and we had to fall back on unblinded data.

As with VenUS I and VenUS II, questionnaire response rates fell over time (they were 89%, 84%, 81% and 86% at 3, 6, 9 and 12 months, respectively). In addition, the questionnaire completion rate (i.e. the proportion of each questionnaire that was fully completed) fell. This meant that at 12 months almost 50% of HRQoL data were unavailable. This was in spite of our efforts to ensure the return of questionnaires (reminders and financial incentives).

Nurse-reported resource data was used in the base case of the economic analysis for several reasons. These data are prospectively and comprehensively collected by the health-care professional and are thus expected to be more accurate and unbiased. In contrast, patient-reported data are subject to individuals' recollection of health-care resource use over the past 3 months. Additionally, patient self-reported data were found to have a high rate of missing values, especially as follow-up time increased. Patient data do not provide enough detail to allow direct calculation of costs associated with treatments, and this was derived from nurse-reported data. However, patient-reported resource use included other information on health-care consultations, e.g. doctor consultations and hospital outpatient visits. Therefore patient data may be more comprehensive in evaluating ulcer-related costs. For this reason, the use of patient-reported data to inform resource use (health-care consultations) was explored in sensitivity analyses to ensure that the results were not due to us using either nurse or patient data alone.

We identified in the 'Executive summary, Existing evidence for the effect of ultrasound healing' that a number of ultrasound regimens have been evaluated in the past, and in designing this study we sought to identify a regimen that was credible. As most evidence was available for the combination of ultrasound at 1 MHz and 0.5 W/cm², including the best-quality study to date (with only moderate risk of bias), we selected this regimen. We were unable to base our selection of regimen on dose-response studies (as none exist) or other robust evidence, and, hence, we can only report on the effects of this particular ultrasound regimen and not higher doses or longer durations of treatment.

Generalisability of the results

VenUS III recruited from 12 centres across England, Scotland, Northern Ireland and Ireland. The sites had various models of delivering leg ulcer care. The inclusion of outpatient clinics, community tissue viability services and district nursing teams means that we can be confident that these results are broadly generalisable, i.e. that the study has external validity across the UK and probably Europe.

Implications for health care

There is no evidence from this trial that low-dose ultrasound should be used for venous leg ulcers that are $> 5 \text{ cm}^2$ and/or older than 6 months, i.e. those described as 'harder to heal'. We evaluated only a specific ultrasound treatment regimen and therefore these results cannot be extrapolated to other regimens.

Implications for research

We identified a large variation in healing rates according to trial centres, with those centres recruiting more patients to the trial having higher healing rates overall. This centre effect may be a manifestation of a relationship between the volume of throughput and the quality of care, such that centres with higher patient throughput may have the opportunity to develop greater expertise in patient assessment, in compression bandage application and in accessing specialist services of vascular surgery, dermatology, orthotics, etc. We controlled for ulcer area and duration; hence, the difference in healing rates across centres is not likely to be due to these prognostic factors being distributed differently across sites (i.e. larger/old ulcers in one site). This interesting finding is worthy of more exploration in future research.

Acknowledgements

Huge thanks are due to the participants for taking part in this trial, research nurses, tissue viability teams, district nurses and hospital outpatient staff for recruiting participants and completing the trial documentation, principal investigators at each site for co-ordinating participant recruitment and the Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC) members for overseeing the study.

We would specifically like to thank

Una Adderley, Paul Allcoat, Jacqui Ashton, Annemarie Brown, Carol Dealey, Sharon Hailes, Linda McDermott-Scales, Janet McGowan, Angie Oswald, Sarah Pankhurst, Nikki Stubbs and Anne Witherow who were the nurse leads in each site. In addition, we would like to thank Bernie Boyle, Susan Bradley, Melanie Burrows, Margaret Crookes, Joanne Dakin, Patricia Davies, Erica Denton, Mary Doherty, Sarah Fiori, Gemma Hancock, June Jones, Peter Jones, Denise Nightingale, Lesley Marland, Jeanette Marshall, Jane Mayes, Jane Megson, Sue Merryweather, Carol Muir, Pam Ross, Rebecca Stubbs, Debra Vickery, Victoria Warner, Shirley Williams and Lindsey Worstenholme for recruiting patients into the study.

Una Adderley, Gemma Hancock and Susan O'Meara undertook the blinded outcomes assessment of clinical ulcer photographs and Mei-See Man carried out the ulcer tracing measurements.

Collaborations and contributions of the authors

The VenUS III collaborators (current and past) are Martin Bland, Sue Collins, Ling-Hsiang Chuang, Ben Cross, Nicky Cullum, Jo Dumville, Kate Flemming, Liz Holey, Cynthia Iglesias, Arthur Kang'ombe, Andrea Nelson, Stephen Pye, Elizabeth Scanlon, Marta Soares, Gerben ter Riet, David Torgerson, Kath Vowden, Peter Vowden, Michael Walker, Shernaz Walton, Val Wadsworth, Judith Watson and Gill Worthy.

EAN was the chief investigator, chaired the Trial Management Group and edited and approved the final draft of the report. JMW was the trial co-ordinator. GW and MB designed the clinical analysis. MB oversaw the conduct of the analysis. AK conducted the clinical analysis. MS contributed to the trial management group, designed the economic analyses and oversaw the conduct of the analysis. L-HC undertook the economic analysis. CI participated in the design and conduct of the study. NAC and DJT contributed to the study design and co-ordination.

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Professor S Homer-Vanniasinkam (Chairperson of TSC January 2006 to December 2006).
Dr Su Mason (member of TSC January 2006 to December 2006, then Chairperson of TSC January 2007 to end).
Professor Kevin Burnand (member of TSC January 2006 to August 2008).
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References

1. Graham ID, Harrison MB, Nelson EA, Lorimer K, Fisher A. Prevalence of lower-limb ulceration: a systematic review of prevalence studies. *Adv Skin Wound Care* 2003;**16**:305–16.
2. Dale JJ, Callam MJ, Ruckley CV, Harper DR, Berrey PN. Chronic ulcers of the leg: a study of prevalence in a Scottish community. *Health Bull (Edinb)* 1983;**41**:311–14.
3. Moffatt C, Martin R, Smithdale R. *Leg ulcer management*. Oxford: Blackwell Publishing Ltd; 2007.
4. Ågren MS, Gottrup F. Causation of venous leg ulcers. In Morison MJ, Moffatt CJ, Franks PJ, editors. *Leg ulcers – a problem-based learning approach*. Edinburgh: Mosby Elsevier; 2007. pp. 141–54.
5. Roe B, Cullum N, Hamer C. Patients' perceptions of chronic leg ulceration. In Cullum NA, Roe BH, editors. *Leg ulcers: nursing management*. London: Balliere Tindall; 1995. pp. 125–34.
6. O'Meara S, Cullum NA, Nelson EA. Compression for venous leg ulcers. *Cochrane Database Syst Rev* 2008; Issue 4, Art No. CD000265. DOI: 10.1002/14651858.CD000265.pub2.
7. Iglesias C, Nelson EA, Cullum NA, Torgerson DJ, for the VenUS Team. The VenUS I trial: a randomised comparison of 4-layer and short-stretch bandages for the treatment of venous leg ulcers. *Health Technol Assess* 2004;**8**(29).
8. Margolis DJ, Berlin JA, Strom BL. Which venous leg ulcers will heal with limb compression bandages? *Am J Med* 2000;**109**:15–19.
9. Lambourne LA, Moffatt CJ, Jones AC, Dorman MC, Franks PJ. Clinical audit and effective change in leg ulcer services. *J Wound Care* 1996;**5**:348–51.
10. Vowden KR, Barker A, Vowden P. Leg ulcer management in a nurse-led, hospital-based clinic. *J Wound Care* 1997;**6**:233–6.
11. Laing W. *Chronic venous diseases of the leg*. London: Office of Health Economics; 1992. pp. 1–44.
12. Morrell CJ, Walters SJ, Dixon S, Collins KA, Brereton LM, Peters J, *et al*. Cost effectiveness of community leg ulcer clinics: randomised controlled trial. *BMJ* 1998;**316**:1487–91.
13. Ragnarson Tennvall G, Hjelmgren J. Annual costs of treatment for venous leg ulcers in Sweden and the United Kingdom. *Wound Repair Regen* 2005;**13**:13–18.
14. Department of Health. *Prescription cost analysis data England, 2006*. London: Department of Health; 2007.
15. Callam MJ, Ruckley CV, Harper DR, Dale JJ. Chronic ulceration of the leg: extent of the problem and provision of care. *Br Med J* 1985;**290**:1855–6.
16. Hickie S, Ross S, Bond C. A survey of the management of leg ulcers in primary care settings in Scotland. *J Clin Nurs* 1998;**7**:45–50.
17. Dyson M. Adjuvant therapies: ultrasound, laser therapy, electrical stimulation, hyperbaric oxygen and vacuum-assisted closure therapy. In Morison MJ, Moffatt CJ, Franks PJ, editors. *Leg ulcers – a problem-based learning approach*. Edinburgh: Mosby Elsevier; 2007.
18. ter Haar G. Therapeutic ultrasound. *Eur J Ultrasound* 1999;**9**:3–9.
19. Watson T. Ultrasound in contemporary physiotherapy practice. *Ultrasonics* 2008;**48**:321–9.

20. Speed CA. Therapeutic ultrasound in soft tissue lesions. *Rheumatology* 2001;**40**:1331–6.
21. Baker KG, Robertson VJ, Duck FA. A review of therapeutic ultrasound: biophysical effects. *Phys Ther* 2001;**81**:1351–8.
22. ter Haar G. Basic physics of therapeutic ultrasound. *Physiotherapy* 1987;**73**:110–13.
23. Enraf Nonius. *Ultrasound therapy*. Delft: Enraf-Nonius BV; 1995.
24. Eriksson SV, Lundeberg T, Malm M. A placebo controlled trial of ultrasound therapy in chronic leg ulceration. *Scand J Rehabil Med* 1991;**23**:211–13.
25. Lundeberg T, Nordstrom F, Brodda-Jansen G, Eriksson SV, Kjartansson J, Samuelson UE. Pulsed ultrasound does not improve healing of venous ulcers. *Scand J Rehabil Med* 1990;**22**:195–7.
26. Roche C, West J. A controlled trial investigating the effect of ultrasound on venous ulcers referred from general practitioners. *Physiotherapy* 1984;**70**:475–7.
27. Dyson M, Franks C, Suckling J. Stimulation of healing of varicose ulcers by ultrasound. *Ultrasonics* 1976;**14**:232–6.
28. Weichenthal M, Mohr P, Stegmann W, Brietbart EW. Low-frequency ultrasound treatment of chronic venous ulcers. *Wound Repair Regen* 1997;**5**:18–22.
29. Callam MJ, Harper DR, Dale JJ, Ruckley CV, Prescott RJ. A controlled trial of weekly ultrasound therapy in chronic leg ulceration. *Lancet* 1987;**330**:204–6.
30. Peschen M, Vanscheidt W. Low frequency ultrasound of chronic venous leg ulcers as part of an out-patient treatment. *Proceedings of the 5th European Conference on Advances in Wound Management* 1996: 271.
31. Franek A, Chmielewska D, Brzezinska-Wcislo L, Slezak A, Blaszczyk E. Application of various power densities of ultrasound in the treatment of leg ulcers. *J Dermatolog Treat* 2004;**15**:379–86.
32. Flemming K, Cullum N. Therapeutic ultrasound for venous leg ulcers. *Cochrane Database Syst Rev* 2000; Issue 4, Art No. CD001180. DOI: 10.1002/14651858.CD001180.
33. RCN Institute, Centre for Evidence Based Nursing, University of York and School of Nursing Midwifery and Health Visiting, University of Manchester. *Clinical practice guidelines. The management of patients with venous leg ulcers. Recommendations for assessment, compression therapy, cleansing, debridement, dressing, contact sensitivity, training/education and quality assurance*. London: Royal College of Nursing Institute; 1998.
34. Margolis DJ, Berlin JA, Strom BL. Risk factors associated with the failure of a venous leg ulcer to heal. *Arch Dermatol* 1999;**135**:920–6.
35. Gardner SE, Frantz RA, Troia C, Eastman S, MacDonald M, Buresh K, *et al*. A tool to assess clinical signs and symptoms of localized infection in chronic wounds: development and reliability. *Ostomy Wound Manage* 2001;**47**:40–7.
36. Taylor R. ‘Mouseeyes’: an aid to wound measurement using a computer. *J Wound Care* 1997;**6**:123–6.
37. Simon D, Freak L, Williams I, McCollum C. Progression of arterial disease in patients with healed venous ulcers. *J Wound Care* 1994;**3**:179–80.
38. Skene AI, Smith JM, Dore CJ, Charlett A, Lewis JD. Venous leg ulcers: a prognostic index to predict time to healing. *BMJ* 1992;**305**:1119–21.

39. Callam M. Prevalence of chronic leg ulceration and severe chronic venous disease in western countries. *Phlebology* 1992;**1**:6–12.
40. Jenkinson C, Layte R. Development and testing of the UK SF-12 (short form health survey). *J Health Serv Res Policy* 1997;**2**:14–18.
41. Kind PT. The EuroQol instrument: an index of health-related quality of life. In Spilker B, editor. *Quality of life and pharmacoeconomics in clinical trials*. Philadelphia, PA: Lippincott-Raven; 1996.
42. ter Riet G. Problems in the conduct of a randomised controlled trial. *J Wound Care* 1998;**7**:259–62.
43. Pye S. Ultrasound therapy equipment: does it perform? *Physiotherapy* 1996;**78**:263–7.
44. Dumville JC, Worthy G, Bland JM, Cullum N, Dowson C, Iglesias C, *et al.* Larval therapy for leg ulcers (VenUS II): randomised controlled trial. *BMJ* 2009;**338**:b773.doi:10.1136/bmj.b773.
45. Kantor J, Margolis DJ. A multicentre study of percentage change in venous leg ulcer area as a prognostic index of healing at 24 weeks. *Br J Dermatol* 2000;**142**:960–4.
46. Etris MB, Pribble J, LaBrecque J. Evaluation of two wound measurement methods in a multi-center, controlled study. *Ostomy Wound Manage* 1994;**40**:44–8.
47. Iglesias CP, Birks Y, Nelson EA, Scanlon E, Cullum NA. Quality of life of people with venous leg ulcers: a comparison of the discriminative and responsive characteristics of two generic and a disease specific instruments. *Qual Life Res* 2005;**14**:1705–18.
48. Ware JE, Kosinski N, Keller SD. The 12-Item Short-Form Health Survey (SF-12): construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;**34**:220–33.
49. Jenkinson C, Layte R, Jenkinson D, Lawrence K, Peterson S, Paice C, *et al.* A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? *J Public Health Med* 1997;**19**:179–96.
50. Iglesias CP, Birks YF, Torgerson DJ. Improving the measurement of quality of life in older people: the York SF-12. *QJM* 2001;**94**:695–8.
51. Walker NK. *Epidemiological studies of leg ulcers in Auckland, New Zealand*. PhD thesis. Auckland: University of Auckland; 2000.
52. Iglesias CP, Birks YF, Torgerson DJ. Increasing response rates to postal questionnaires. Changing layout of questionnaires increases response rates. *BMJ* 2002;**325**:444.
53. Kind P, Hardman G, Macran S. *UK population norms for EQ-5D*. Centre for Health Economics discussion paper 172. York: Centre for Health Economics, University of York; 1999.
54. Edwards P, Roberts I, Clarke M, DiGuiseppe C, Pratap S, Wentz R, *et al.* Methods to increase response rates to postal questionnaires. *Cochrane Database Syst Rev* 2007; Issue 3, Art No. MR000008. DOI: 10.1002/14651858.MR000008.pub4.
55. Majeske C. Reliability of wound surface area measurements. *Phys Ther* 1992;**72**:138–41.
56. Collett D. *Modelling survival data in medical research*. 2nd edn. Boca Raton, FL: Chapman & Hall/CRC Press LLC; 2003.
57. Billingham LJ, Abrams KR. Simultaneous analysis of quality of life and survival data. *Stat Methods Med Res* 2002;**11**:25–48.

58. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. *Methods for the economic evaluation of health care programmes*. 3rd edn. Oxford: Oxford University Press; 2005.
59. StataCorp. *STATA statistical software: release 10.1*. CollegeStation, TX: STATA Corporation; 2008.
60. Willan AR, Lin DY, Manca A. Regression methods for cost-effectiveness analysis with censored data. *Stat Med* 2005;**24**:131–45.
61. Dumville J, Worthy G, Soares M, Bland JM, Cullum M, Dowson C, *et al*. VenUS II: a randomised controlled trial of larval therapy in the management of leg ulcers. *Health Technol Assess* 2009;**13**(55).
62. Brook R. EuroQol: the current state of play. *Health Policy* 1996;**37**:53–72.
63. The MVH Group. *The measurement and valuation of health: first report on the main survey*. York: Centre for Health Economics, University of York; 1994.
64. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *BMJ* 1990;**300**:230–5.
65. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005;**14**:487–96.
66. Gold M, Siegel J, Russell L, Weinstein M. *Cost-effectiveness in health and medicine*. Oxford: Oxford University Press; 1996.
67. National Institute for Health and Clinical Excellence. *Guide to the methods of technology appraisal*. London: National Institute for Health and Clinical Excellence; 2008.
68. British Medical Association/Royal Pharmaceutical Society of Great Britain. *British national formulary*. No. 54, September 2007. London: BMA and RPS; 2007.
69. Personal Social Service Research Unit (PSSRU). *Unit costs of health and social care 2008*. Canterbury: University of Kent; 2008.
70. Claxton K. The irrelevance of inference: a decision making approach to the stochastic evaluation of health care technologies. Reprinted in: Culyer A, editor. *Health economics: critical perspectives on the world economy*. London: Routledge; 2007.
71. Efron B, Tibshirani R. *An introduction to the bootstrap*. London: Chapman & Hall; 1993.
72. Van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and c/e-ratios alongside a clinical trial. *Health Econ* 1994;**3**:309–19.
73. Brealey S, Atwell C, Bryan S, Coulton S, Cox H, Cross B, *et al*. The DAMASK trial protocol: a pragmatic randomised trial to evaluate whether GPs should have direct access to MRI for patients with suspected internal derangement of the knee. *BMC Health Serv Res* 2006;**6**:133.
74. Watson J, Helliwell P, Morton V, Adebajo A, Dickson J, Russell I, *et al*. Shoulder acute pain in primary healthcare: is retraining effective for GP principals? SAPPHIRE – a randomised controlled trial. *Rheumatology* 2008;**47**:1795–802.
75. Kleinbaum D, Klein M. *Survival analysis, a self-learning text*. New York, NY: Springer Science + Business Media, Inc.; 1997.
76. Al-Kurdi D, Bell-Syer SEM, Flemming K. Therapeutic ultrasound for venous leg ulcers. *Cochrane Database Syst Rev* 2008; Issue 1, Art No. CD001180.
77. Akbari Sari A, Flemming K, Cullum NA, Wollina U. Therapeutic ultrasound for pressure ulcers. *Cochrane Database Syst Rev* 2006; Issue 3, Art. No. CD001275. DOI: 10.1002/14651858.CD001275.pub2.

78. Cullum N, Nelson EA, Flemming K, Sheldon T. Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy. *Health Technol Assess* 2001;5(9).
79. Busse JW, Kaur J, Mollon B, Bhandari M, Tornetta P III, Schünemann HJ, *et al.* Low intensity pulsed ultrasonography for fractures: systematic review of randomised controlled trials. *BMJ* 2009;338:b351, doi: 10.1136/bmj.b351.
80. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, *et al.* The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134:663–94.
81. Department of Health *Medicines for human use (clinical trials) regulations 2004*. URL: www.uk-legislation.hmso.gov.uk/si/si2004/20041031.htm (accessed March 2005).

Appendix 1

Study protocol

VenUS III (Venous Ulcer Studies III)

Ultrasound for venous leg ulcers

Protocol version 6.0

March 2006

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2 Amendments to protocol since August 2004

2.1 Inclusion/exclusion

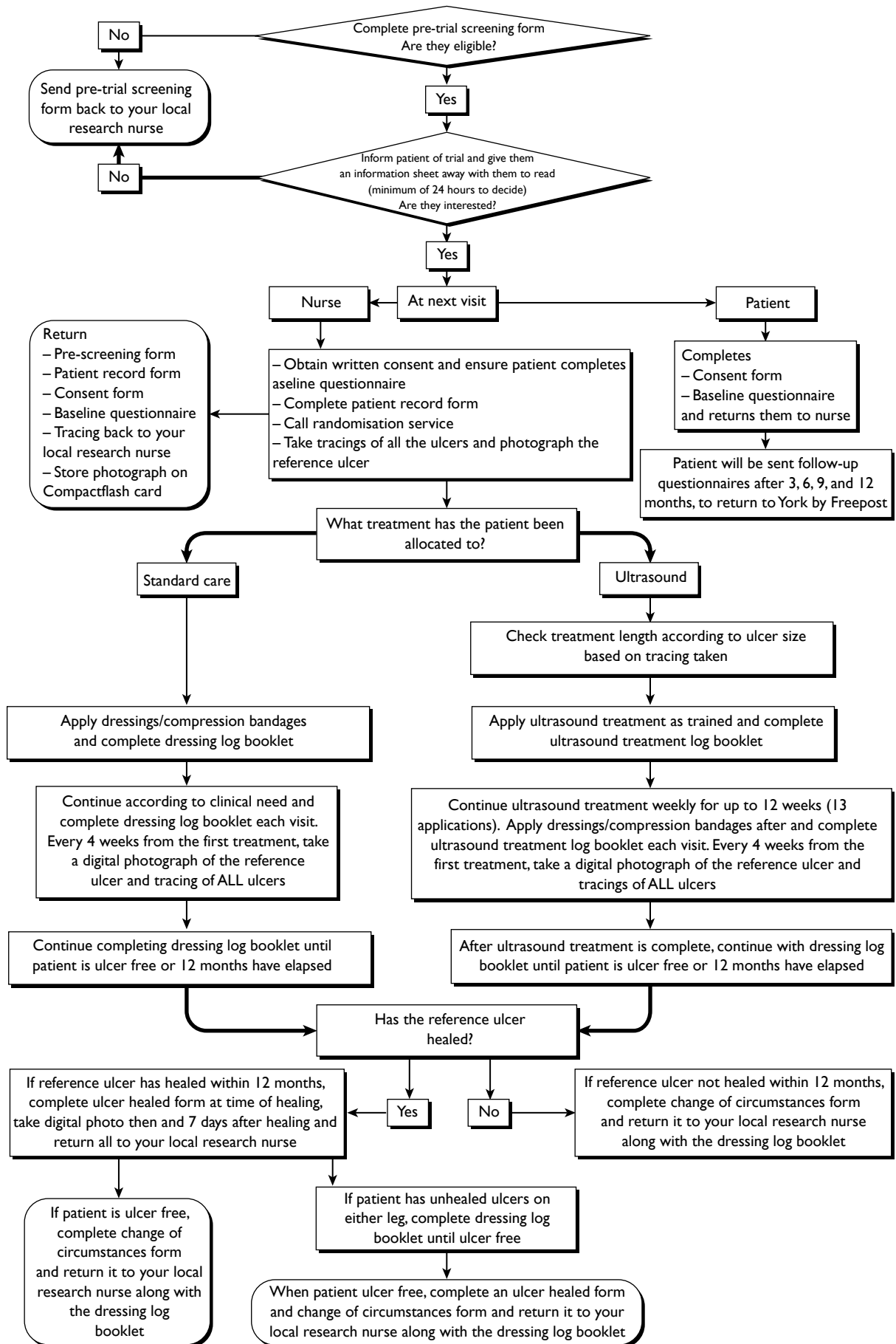
1. We have dropped the exclusion criterion 'rheumatoid arthritis'. Investigators made a strong case that many people can have venous ulcers in the presence of rheumatoid arthritis and that ulcer is not necessarily due to their rheumatoid disease. We initially excluded this population as they may be more prone to compression damage but given that the clinicians caring for these patients commonly use high compression, then we decided to include them.
2. We have dropped the exclusion criterion 'diabetes'. Clinical collaborators have argued that people can have venous ulcers in the presence of diabetes mellitus, and that their ulcer may not be secondary to diabetes. We initially excluded this population as according to National Clinical Practice Guidelines, they would not be suitable for high compression, but we are informed that in some clinical centres expert practitioners will treat people with well-controlled diabetes, who have had a vascular assessment, with high compression therapy. Well-controlled diabetes is defined as a recent HbA_{1c} level of < 10%.
3. We have dropped the exclusion criterion peripheral arterial disease, as this is unnecessary as the inclusion criterion states that the ulcer must be primarily due to venous disease. The clinician has considered someone for the trial as the patient has a clinical diagnosis of 'ulcer primarily due to venous insufficiency', and the ABPI reading confirms the lack of significant arterial insufficiency.
4. We have gained ethical approval to recruit people with venous ulceration and an ABPI of at least 0.8 who are unable to tolerate high compression therapies. Our clinicians argue that some people are tolerant of reduced compression therapy and this population represent a particular challenge to heal, as high compression therapy is the single most effective element of treatment.

2.2 Outcome measures

1. We decided to amend the primary outcome measure in the light of advice from the Trial Steering Committee (20 January 2006) and the Trial Management Group (3 March 2006).
Rationale:
Initially we had the primary outcome measure as complete healing of all ulcers, as this is clinically the time at which leg ulcer treatment can be said to have achieved its ultimate aim, and the patient no longer requires dressings, bandages or nurses visits. However, in this trial the ultrasound is delivered only to the reference (i.e. largest) ulcer, then any outcome measure which relied on the healing of other ulcers remote from this would have the potential to dilute any treatment effect.
2. We will therefore have the primary outcome as complete healing of the ulcer treated with ultrasound (the reference ulcer) and record the time to complete healing of all ulcers as a secondary outcome measure.
3. We have added a digital photograph for confirmation of healing at day of healing and 7 days later. This photograph will be assessed 'blind' at the Trials Unit, for confirmation of healing. We did not ask nurses to take a digital photograph at every visit as we felt this was onerous. Digital photography was not budgeted for in the trial and we have limited resources to provide cameras, however, as many centres have these for the VenUS II trial, we felt that taking healing photographs was important.
4. We confirmed that the patients are followed up until all ulcers are healed as costs to the patient and provider continue until the patient is ulcer free, therefore the economic end points require that we have data on date of complete ulcer healing. In patients with one ulcer, and in those in whom smaller ulcers heal before the largest ulcer heals, then the date of healing of the reference ulcer will be the date of complete ulcer healing.
5. We identified that patient questionnaire return rates in the previous VenUS trials could be improved and therefore we have obtained agreement from collaborators to send £5 as a token 'thank you' payment to patients at the end of the trial, with the final questionnaire. This will not be mentioned in the patient information sheet, so that any possibility that it would be interpreted as a financial incentive to taking part in the trial will be minimised. The final questionnaire, at 12 months post-randomisation will be preceded by a letter notifying the patient that their final trial questionnaire is due to arrive shortly, and that it will be accompanied by a £5 note as a thank you for their taking part in the trial and completing the questionnaires. This letter will make it explicit that the £5 is not conditional on the patient returning the questionnaire.
6. We identified, after discussion with the manufacturers of the ultrasound machines, that 6 monthly checks of the ultrasound machines may be unnecessary as the amount of drift is related to usage of the machines, and each machine will be used for an average of 9 hours (over 2 years) during the trial. They therefore suggested yearly testing was sufficient. We propose to test machines at 3 months, using an ultrasound balance, and if the readings indicate that the machine output is within tolerance, then recheck every 6 months.

2.3 Minor amendments/typographical errors

1. Protocol clarified to reflect that an ankle brachial pressure index (ABPI) of 0.8 or greater is acceptable for definition of non-clinically significant arterial insufficiency. The previous protocol stated ABPI had to be > 0.8 . National clinical practice guidelines recommend that compression is used on people with venous ulceration and an ABPI of 0.8 or greater, and this amendment reflects national guidance and local treatment protocols.
2. Protocol amended to clarify that the research objective proportion of ulcers healed at 12 months should read 'the proportion of *patients with* ulcers healed at 12 months'.



3 Trial identifier

3.1 Full title of trial

Randomised controlled trial of cost-effectiveness of ultrasound for 'hard-to-heal' venous ulcers

3.2 Acronym

VenUS III (Venous Ulcer Studies III)

4 Background to the trial

4.1 Leg ulceration

Leg ulceration is a chronic, relapsing, and remitting condition, affecting 15–18/1000 adults in industrialised countries.¹ It has a significant personal impact on older people's health and quality of life (QoL).^{2,3} Venous leg ulcers represent up to 84% of all leg ulcer cases in developed countries.³ The total cost of leg ulcer management in the UK in 1989 was estimated to be between £150M and £600M per annum, with more than 60% of this cost attributed to community-based nursing services.⁴ The only therapy so far shown to be clearly effective in the treatment of venous leg ulcers is compression bandaging or hosiery, with high compression being more effective than low compression (relative risk of healing 1.5, 95% CI 1.2 to 2.0).⁵ Small (<5 cm² area) and new (<6 months duration) ulcers treated with high compression heal quickly; in our recent trial of compression, the median time to healing of ulcers with pre-trial duration of <6 months, was 77 days.⁶ New ulcers treated with high compression, therefore, heal without the need for adjuvant therapies. One high-quality prognostic study has found that 95% of venous ulcers that are both small (<5 cm²) and new (<6 months duration), if treated with high compression (Unna's boot, the standard system in the USA), can be expected to heal within 6 months (95% CI 75% to 99%).⁷ Audits of healing times using the UK standard compression system (four-layer high compression) confirm the importance of ulcer area and duration in predicting healing at 6 months.^{8,9} The challenge is now to increase the proportion of ulcers healed (20% remained unhealed in VenUS I at 12 months)⁶ and to decrease the time to healing, particularly amongst people with longstanding ulceration or large ulcers.

4.2 Ultrasound

Longitudinal waves with a frequency between 20 hertz (Hz) and 20,000 Hz can be heard, however humans cannot detect frequencies below 20 Hz; these are described as 'subsonic', nor those above 20,000 Hz, described as 'ultrasonic'. In clinical practice, the frequencies for ultrasound treatment are typically between 700,000 Hz and 4,000,000 Hz [0.7–4.0 megahertz (MHz)]. As ultrasound penetrates the skin tissues, absorption of the energy wave means that the intensity of ultrasound decreases as the wave travels into the tissues. The amount of absorption depends on the nature of the tissues and on the intensity of the ultrasound. The absorption coefficient of ultrasound in soft tissue increases linearly with frequency, so using higher frequencies (say 3 MHz rather than 1 MHz), reduces the penetration depth, by about one third (from 37 mm to 12 mm in skin).¹⁰

4.2.1 Effect of ultrasound on tissues

When skin is exposed to ultrasound (insonated), there is a transfer of the energy from the ultrasound waveform to the tissues. Researchers have described a number of physiological responses to the biophysical effects of therapeutic ultrasound, and the research has been critically reviewed by Baker *et al.*¹¹ Many of the investigations of the biophysical effects of ultrasound have been in vitro studies and there is relatively little evidence that these changes occur in vivo. Biophysical effects of ultrasound have traditionally been separated into thermal and non-thermal effects, though Baker *et al.* points out that this distinction is artificial, as at low doses, where

non-thermal effects are said to predominate, there will always be some transfer of thermal energy.¹¹ At high doses, where thermal effects are said to predominate there will always be both non-thermal and thermal effects.

Non-thermal effects

Ultrasound vibrations transmitted to the skin cause compression and expansion in the tissues at the same frequency as the applied ultrasound, leading to areas of high and low pressure in the tissues. The effects of these small movements in the tissues are poorly understood. Ultrasound is also said to cause cavitation (development of small gas bubbles in the tissues)¹⁰ and acoustic streaming (localised liquid flow around a vibrating bubble).¹² Baker *et al.* argues that there is no evidence from in vivo studies in humans that cavitation occurs at the ultrasound doses used for tissue repair.¹⁰ Given the absence of cavitation, except in gas filled cavities (such as the lungs), it is further argued that acoustic streaming does not occur in vivo. The way in which cavitation or acoustic streaming might contribute to tissue repair is not obvious; it is postulated that they might lead to reversible changes in the cell membrane permeability.¹³ In vitro studies have demonstrated that there are changes in cell membrane permeability during ultrasound exposure, but it is not clear if these findings also occur in vivo, or what impact they would have on healing.¹³

Thermal effects

Absorption of ultrasound in the tissues may lead to frictional heat, which in animal models has been shown to increase the local temperature by up to 5 °C.¹⁴ Clearly too much heating could lead to local burns, and it is unclear whether a heating effect is beneficial, and if so, how much local heating is effective and safe. The problem of excess heat is reduced when using pulsed ultrasound as the effective intensity is lower and some of the heat is dissipated between the pulses.¹²

4.2.2 Ultrasound application

There are a number of ways of delivering ultrasound to the skin tissues, mainly treatment under water or direct contact, viz.:

- directly to the area of injury – the ultrasound is directed at the area of tissue for healing
- indirect – the ultrasound is applied to an area away from the target point, and is transmitted to that area by direct transmission, reflection, and refraction (e.g. application of ultrasound to opposite side of leg from an ulcer; application in a water bath with transmission through water).

4.2.2.1 Dose

Dose of ultrasound delivered is related to both stimulus strength [intensity, expressed as watts (W)/ centimetre (cm)²] and the duration of treatment. A number of factors make it difficult to apply precise doses of ultrasound to the tissues. The output wave is not uniform across the width of the beam; the degree of variation across the beam is described in the beam non-uniformity ratio (BNR). Also, because of differences in the ability of different tissues to absorb ultrasound and because of reflection and refraction of the ultrasound beam in the tissues, the amount of ultrasound energy delivered to the treated area is not easily predicted from the applied dosage. The treatment head is kept in motion in an effort to minimise the variations in ultrasound energy delivered throughout the target area. In this trial we will use a standard duration of treatment (according to the area insonated) and deliver a stimulus strength of 0.5 W/cm². This will allow us to describe accurately the 'effective intensity' of ultrasound. Effective intensity will be measured according to current international standards.^{15,16}

4.2.2.2 Contraindications

Ultrasound is contraindicated in people with ankle prostheses/metal anywhere in the foot (e.g. pin and plate, shrapnel), because bone cement used in the replacement of joints has a high absorption capacity, the application of ultrasound to the ankle area may lead to heat damage of the prosthetic joint.¹⁷ Ultrasound is also contraindicated for people with suspected thrombophlebitis (the mechanical vibrations may cause an embolism);¹⁷ people with active cellulitis (potential risk of accelerated growth and dissemination of bacteria throughout the body);¹⁷ in cases of suspected or confirmed local cancer/metastatic disease,¹⁷ and cases of obvious ulcer infection.¹⁷

4.3 Ultrasound and wound healing: the need for a trial

A number of studies have investigated the impact of ultrasound on skin cells (in vitro) and chronic wounds (in vivo). In general there have been few good quality studies demonstrating that any of the 'in-vitro' effects have any clinical importance.¹¹

There have been eight randomised controlled trials (RCTs) of ultrasound for treating venous leg ulcers. Seven of these were summarised in a systematic review by some of the applicants¹⁸ and one additional trial has been published subsequently.¹⁹ The sample sizes in these trials ranged from 12–108 patients and five trials used true randomisation with allocation concealment. The trials made various comparisons of ultrasound versus sham (four trials) or ultrasound as an adjunct to standard care versus standard care alone. Various types of ultrasound at different dose were used. Frequency of ultrasound ranged between 0.3 and 3.0 MHz: 0.3 MHz was used in two trials (applied via water bath), 1.0 MHz was used in four trials and 3.0 MHz was used in another two trials. 1.0 MHz has greater depth penetration than 3.0 MHz. Ultrasound doses ranged between 0.1 and 1.0 W/cm². In two trials in which a water bath ultrasound device was used, 0.1 W/cm² was used. Doses of 0.5 W/cm² were used in three trials and 1.0 W/cm² in four trials (one trial compared 0.5 and 1.0 W/cm² against standard care). No trials reported that they confirmed ultrasound equipment output.

The largest trial (108 people) evaluated weekly ultrasound but the other trials administered ultrasound at two- or three-times a week, with one having a reducing frequency from three- to one-time(s) a week. Four trials used ultrasound for 12 weeks, two for 8 weeks and two for 4 weeks. The five trials that described duration of ultrasound regimen used 10 minutes (three trials) or 5–10 minutes, depending on ulcer area (two trials).

The heterogeneity in these trials with respect to the delivery mode, dose, duration, treatment length and frequency used, means that meta-analysis of all these trials may not be reliable. Another problem with synthesising these studies is the likely difference in the ultrasound actually delivered, even when treatment regimens appear similar due to the differences in output between machines and over time (drift). The Cochrane review undertook meta-analysis of the four trials that reported data on proportion of ulcers healed at 8–12 weeks found that the relative risk of healing with ultrasound was 1.44 (95% CI 1.01 to 2.05). The absolute difference in the risk of ulcers healing in the trials against sham ultrasound was 10% (95% CI –10% to 30%), while in the trials comparing against standard care alone it was 15% (95% CI 0% to 30%). Given that data from only four of the eight trials were pooled, and the potential heterogeneity in the interventions, this meta-analysis must be interpreted cautiously.

Given that standard care of venous ulcers, using high compression and simple dressings heals around 80% of all ulcers with 12 months, then ultrasound as an adjuvant therapy is likely to be reserved for those resistant to standard therapy, or are identified at the outset as 'hard to heal'.

5 Research objectives

To compare the clinical effectiveness and cost-effectiveness low-dose ultrasound (0.5 W/cm² spatial average and temporal peak) delivered at 1 MHz in conjunction with standard care against standard care alone in the treatment of hard-to-heal venous ulcers. The trial will assess whether the addition of 5–10 minutes of ultrasound (depending on ulcer area) to a package of best available practice affects:

- the time to healing of venous leg ulcers
- the proportion of patients with ulcers healed at 12 months
- health-related quality of life (HRQoL)
- the costs of caring for venous leg ulcers.

Ultrasound machines with regularly verified output will be used to allow valid inferences of the effect of the applied dose.

5.1 Research methods

5.2 Study design

A multicentre, pragmatic, RCT with an economic evaluation, comparing low-dose ultrasound with standard care in hard-to-heal venous ulcers.

5.2.1 Case definition

Only people with 'hard-to-heal' venous leg ulcers will be recruited into this study.

Venous ulceration

For the purpose of this study a leg ulcer will be considered to be any break in the skin on the leg (below the knee), which has either (a) been present for more than 6 weeks or (b) occurs in a person with a history of venous leg ulceration. A participant will be considered to have a purely venous leg ulcer where there is no other causative aetiology, the ulcer appears clinically venous (moist, shallow, irregular shape, venous eczema, ankle oedema, and/or lipodermatosclerosis, not confined to the foot), and the study participant has an ABPI of >0.8. An ABPI <0.8 indicates that there is a high probability that arterial insufficiency is present and that the ulcer should not be regarded as venous.²⁰

Hard-to-heal ulceration

Prognostic studies have found that patients with ulcers > 5 cm² and duration > 6 months are less likely to heal within 24 weeks.²¹ For a person to be included in the trial they must either:

- (a) have a venous ulcer of > 6 months duration (determined by asking the patient), or
- (b) have a venous ulcer larger than 5 cm² (estimated by tracing the ulcer outline onto a transparent grid with 1 cm lines; nurse training will include standard tracing techniques/ calculation of area).

Patients with ulcers that fulfil both criteria (> 5 cm² and present of more than 6 months) are also eligible.

5.2.2 Inclusion criteria

All people with venous leg ulcers are potentially eligible for inclusion in the proposed trial if they meet the following criteria:

- (a) Currently receiving care from community/leg ulcer/out-patients nurses in trial centres.
- (b) Able to give written informed consent to participate in the study. Information sheets and consent forms will be provided in languages other than English if required.
- (c) The primary cause of their ulcer is chronic venous insufficiency. This diagnosis will be made using the same diagnosis criteria currently employed by caregivers in the community, namely the clinical appearance of the ulcer, patient history and an ABPI to rule out arterial insufficiency.²⁰
- (d) Have 'hard-to-heal' ulcers as defined by the presence of at least one of these criteria:
 - (e) a venous ulcer of > 6 months duration,
 - (f) a venous ulcer larger than 5 cm².
 - (g) Doppler-determined ABPI of at least 0.8 within last 3 months.
- (h) People with an ulcer infection (based on a clinical signs and symptoms checklist) at baseline will be eligible to participate once the infection has resolved.²⁴
- (i) People who are unable to self-complete the English language QoL tools will still be eligible to participate, but we will not collect QoL data from them [the Short Form questionnaire-12 items (SF-12) is validated in English, Spanish, Italian, French and German and we anticipate that the number of non-English speakers who use these languages will be very small].

5.3 Exclusion criteria

Potential participants will be excluded if they meet the following criteria:

- (a) Their leg ulcer is due to causes other than venous insufficiency (e.g. arterial insufficiency, malignancy).
- (b) The patient has poorly controlled diabetes, as evidence by a glycolated haemoglobin (HbA_{1c}) of > 10%.
- (c) People with ankle prostheses/metal anywhere in the foot (e.g. pin and plate): because bone cement used in the replacement of joints has a high absorption capacity, the application of ultrasound to the ankle area may lead to heat damage of the prosthetic joint.¹⁷
- (d) People with suspected thrombophlebitis: the mechanical vibrations may cause an embolism.¹⁷
- (e) People with active cellulitis: because of the potential risk of accelerated growth and dissemination of bacteria throughout the body.¹⁷
- (f) In cases of suspected or confirmed local cancer/metastatic disease.¹⁷

5.4 Patient recruitment

Patients with venous leg ulcers will be recruited from the following clinical centres:

1. Hull
2. Leeds
3. West Cumbria
4. Bradford
5. Altnagelvin (Londonderry)
6. Selby and York
7. Bolton
8. other centres as required.

Local nursing staff or clinical research nurses (CRNs) will identify potential participants, and will supply them with an information sheet about the trial. Patients will be given a minimum of 24 hours to read the information sheet and consider participation. A research or community/leg ulcer nurse will visit those patients that agree to participate, and at the enrolment visit will:

- (a) obtain written consent from them to participate in the trial

- (b) record baseline data
- (c) telephone the freephone randomisation service to randomise patient
- (d) administer first ultrasound treatment, if appropriate, and reapply compression bandages.

5.5 Randomisation

Research or community nurses from each study centre will enter patients into the trial by calling a freephone central randomisation service provided by the Trials Unit in York. The following information will be collected at randomisation from the nurse:

1. patient details including full name, gender, date of birth, full postal address
2. trial centre
3. whether ulcer is smaller or larger than 5 cm²
4. whether ulcer has been present for more or < 6 months
5. confirmation of eligibility (including use of high compression therapy)
6. confirmation of written informed consent.

Participants will be randomised by computer in equal proportions, block sizes randomly of size four and six. There will be no stratification.

5.5.1 Non recruitment

Clinical research nurses will be asked to complete a screening form for all patients with venous ulcers who present to the local service. For people who are not eligible to enter the trial, these forms will be returned to the York Trials Unit. Information collected will be all reasons patient is not eligible/decided not to consider trial recruitment, as well as patient date of birth, gender, and date of consideration for trial entry.

6 Data collection

Research, community/leg ulcer or outpatients nurses will collect baseline data from each participant, prior to randomisation. The patient's regular nurse will undertake the assessment of the primary outcome (time to healing) and take a digital photograph at this time, every 4 weeks, at healing (or 12 months, whichever is sooner) and after 7 days post-healing (if healed). Research nurses will collect recurrence data at 6 and 12 months.

Health-related quality of life (HRQoL) data will be collected via postal survey at 3, 6, 9 and 12 months. We will monitor response rates in VenUS II and VenUS III trials and if necessary, reduce the number of assessments in order to increase response rates (*Table 1*).

TABLE 1 Time points for data collection

Visit	Time	Assessments
Pre	-7 to 0 days	Screening, baseline assessment, including ulcer assessment by digital photograph and tracing
1	0 days	Randomisation and commencement of ultrasound treatment
2	3 months	Assessment of QoL, end of ultrasound treatment
3	6 months	Assessment of recurrence and QoL
4	9 months	Assessment of QoL
5	12 months	Assessment of recurrence and QoL
	Monthly until ulcer healed or 12 months (which ever is sooner)	Assessment of ulcer area by digital photographs and tracings, costs, non-trial treatments, and adverse events

6.1.1 Baseline measurements

Study centres: Altnagelvin, Bradford, Hull, Leeds, West Cumbria etc.

Demographic data: age, sex.

Clinical history: incident or recurrent ulcer, duration of ulcer disease, duration of current ulcer (oldest ulcer and reference ulcer if different), mobility, height, weight, ankle circumference.

Prognostic variables: current ulcer duration and ulcer size, as they are predictive of ulcer healing within 24 weeks.⁷ Ulcer area will be determined from a leg ulcer tracing.

Ankle brachial pressure index: a Doppler-determined ABPI will be obtained from clinical records for each participant. ABPI are routinely obtained for all leg ulcer patients. All groups use non-directional Doppler with 8 MHz probes to record arm (brachial) and ankle pressure measurements according to the method described by Vowden *et al.*²⁷ For inclusion in the study, this reading must have been obtained in the last 3 months as readings change over time.²⁸

Health-related quality of life questionnaires: SF-12 and European Quality of Life-5 Dimensions (EQ-5D).

6.1.2 Primary outcome measure

The primary outcome measure in this trial will be time to reference ulcer healed. Healing will be defined as complete epithelialisation in the absence of scab/eschar. Time to healing data will be collected by the local nurse, who will notify the CRN both when the reference ulcer (the largest at recruitment) and when the last ulcer has healed. A photograph of the reference/last ulcer site will be taken at healing and at 7 days post-healing for validation purposes. These photographs will be assessed blind at the York Trials Unit to confirm healing.

6.1.3 Secondary outcome measures

A number of secondary outcome measures will be investigated, viz.:

6.1.3.1 Proportion of patients healed

Measured at 3 and 6 months post-randomisation. This will allow direct comparison of the results with other trials.

6.1.3.2 Percentage and absolute change in ulcer size

Measured at 1, 3 and 12 months post-randomisation. The data collected will allow the determination of reduction in ulcer area in patients who do not achieve complete ulcer healing. If the ultrasound and standard care groups achieve similar times to complete healing but one resulted in larger changes in ulcer area, then this may be clinically important as smaller ulcers are thought to exude less and therefore require less frequent dressing changes. Furthermore the recording of ulcer area at these time points will allow further study of the trajectory of healing for venous leg ulcers and the relationship between the reduction in ulcer area and eventual healing. One study found that increased ulcer area at 1 month after initiation of treatment is a useful predictor for non-healing.²⁹ Identifying patients who are likely to fail to heal early on in treatment allows these patients to have prompt referral to specialist centres for further assessment and treatment. Measurement of ulcer size will involve taking a leg ulcer tracing according to standard procedure – using a comfortable, transparent acetate sheet and a fine-nibbed, indelible pen, taking the outer edge of the ulcer rim as the outer edge of the tracing line (i.e. ulcer area = area enclosed by tracing and area of line). Ulcer area, as determined by acetate tracing, is an accurate and reliable measure.³⁰

6.1.3.3 Proportion of time patients are ulcer free

Reduction in recurrence would help reduce the prevalence of this condition and thus cost. Crude recurrence rates are potentially biased by any difference in healing rates associated with the two groups (ultrasound or standard care), since if one group has more rapid healing, then people in that group are at risk of earlier recurrence. To account for this we will use the proportion of time that patients are ulcer free as the clinically important measure since it is a function of both healing and recurrence and is important for patients. Patients with healed ulcers will be contacted by telephone at 6, 9 and 12 months in order to obtain recurrence data.

6.1.3.4 Costs

Recorded at each visit by a community nurse until the ulcer has healed or for 12 months, whichever is sooner. The nurse will record at each visit the ultrasound delivered (time, dose etc.), the number and type of dressing products, and compression bandages used. This process will facilitate an incremental analysis of the costs of ultrasound with a view to determining cost-effectiveness of ultrasound. Direct costs (hire of ultrasound machine, dressing product, compression bandages, antibiotic use) will not vary by centre, while indirect costs (e.g. depreciation of capital, mileage) and salary will and therefore will not be recorded.

6.1.3.5 Health-related quality of life (HRQoL)

Each person's perception of his or her general health will be assessed using the acute version of the SF-12³² and the EQ-5D.²⁵ The SF-12 is a reliable and well-validated questionnaire,³³ and has been used in UK populations including with older people and leg ulcer patients.^{34,35} SF-12 will be completed at baseline, 3, 6, 9 and 12 months. The EQ-5D is a generic measure of health status, where health is characterised on five dimensions (mobility, self-care, ability to undertake usual activities, pain, anxiety/depression).²⁵ Patients are asked to describe their level of health on each dimension using one of three levels: no problems, moderate problems and severe problems. Each response locates a person into one of 245 mutually exclusive health states, each of which has previously been valued on the 0 (equivalent to dead) to 1 (equivalent to good health) 'utility' scale based on interviews with a sample of 3395 members of the UK public.³⁶ The EQ-5D has been validated in the UK. The QoL questionnaires will be administered to patients by postal survey. The EQ-5D will be administered at baseline, 3, 6, 9 and 12 months.

6.1.3.6 Adverse events

Recorded at each visit by a nurse until the patient is ulcer free or for 12 months, whichever is sooner. Both device related and unrelated events will be recorded. Serious device related adverse events will be reported to the trial co-ordinator within 24 hours and reported to both the trial sponsor and Multicentre Research Ethics Committee (MREC) (as per EN 540).³⁷

6.1.4 Withdrawal

Withdrawal may refer to the following situations; where the patient wishes to withdraw from the study treatment but is prepared to continue answering questions about their ulcer and its effect on their life, and where the patient wishes to withdraw from both the trial treatment and the follow-up. We will ensure that the local nurses and CRNs are aware of the difference in these situations, and that they are explicit about whether patients wish to withdraw from treatment or follow-up.

6.1.5 Loss to follow-up

Loss to follow-up occurs when there is no further data available on a patient during the 12 months post-randomisation. As this population is relatively stable, we anticipate a low loss to follow-up rate (for example VenUS I trial). Despite this, follow-up rates for the completion of questionnaires can drop as patients progress through the trial. However, recent evidence from Edwards *et al.*³⁸ shows that the odds of response to postal questionnaires doubles when a

monetary incentive is used. This almost doubled again when the incentive was non-conditional on response. In addition, the authors found that contacting participants before sending the questionnaire also increased the response. Based on this evidence, we propose to send a letter to participants two weeks prior their final questionnaire informing them of its forthcoming arrival. This final questionnaire will then be posted along with a £5 note as recognition of their commitment to the study. The receipt of this £5 is not conditional on the return of the questionnaire.

7 Planned interventions

Participants will be randomised to receive:

- low-dose (0.5 W/cm²) ultrasound, 1 MHz, with a pulsed pattern of 1:4. The ultrasound will be applied to periulcer skin, weekly for up to 12 weeks, at regular dressing changes, or
- standard care: this will be a simple low-adherent dressing and high compression, four-layer bandaging, reduced compression or no compression, according to the clinical assessment of the level of pressure tolerated by the patient. The nurses will decide on the frequency of bandage change according to clinical need.

7.1 Ultrasound therapy

7.1.1 Preparation for treatment

Prior to the application of the ultrasound the leg will be washed (often immersed in a bucket of tap water). Any loose skin from around the ulcer and remnants of emollients will be removed (these can accumulate on the ultrasound head, making cleaning, and infection control, more difficult). The ultrasound will be applied directly to the skin surrounding the ulcer, with a water based contact gel to ensure passage of the waveform from the transducer to the tissues (ultrasound is reflected from air pockets).

7.1.2 Target ulcer

The patient's regular nurse will administer each ultrasound treatment for 5–10 minutes to the reference ulcer. The reference ulcer is defined as the largest eligible ulcer at the baseline visit.

7.1.3 Concurrent therapy

All dressings and bandages will be replaced at these visits. Concurrent therapy for all patients will be low-adherent dressings and four-layer high compression bandaging, reduced compression or no compression, according to the clinical assessment of the level of pressure tolerated by the patient. Additional visits for ultrasound therapy should not be required as this would increase the number of visits and of bandage applications required (and hence the cost of care).

7.2 Training in and monitoring of application of ultrasound intervention

Prior to the trial starting, participating community nurses will attend a full day training programme on the rationale for the trial, patient eligibility, recruitment procedures (including consent and randomisation), ultrasound treatment application, data collection (completion of trial documentation and tracing ulcer outlines), handling participant withdrawal and adverse event reporting. Competency in ultrasound administration will be assessed at the end of the training day. The CRNs will also cascade training in delivering ultrasound for the purposes of the trial to other local nurses so that treatments can be maintained during holiday periods/staff absences.

Clinical Research Nurses will audit the use of ultrasound within the trial, to check that the ultrasound is being delivered as per protocol, i.e. assessment of area of insonation, preparation of

skin, application of ultrasound, recording treatment delivered, assessment of unwanted effects, etc.

7.3 Calculating ultrasound treatment time

Ulcers of area $< 5 \text{ cm}^2$ will receive 5 minutes ultrasound, those of 10 cm^2 or $< 10 \text{ cm}^2$ will receive 10 minutes ultrasound (the maximum time of treatment). For ulcer areas between 5 and 10 cm^2 , the treatment time in minutes equals the ulcer area in square cm (6 cm^2 means 6 minutes etc.). Ulcer area will be recalculated every 4 weeks.

7.4 Ultrasound machines

The ultrasound machines are supplied, at discounted price, by EMS Physio Ltd, the largest UK manufacturer of ultrasound machines. Their EMS Therasonic 355 Physiotherapy machine delivers only 1 MHz ultrasound.

7.5 Auditing performance of ultrasound machines

The ultrasound machines will be assessed for a check of the intensity of ultrasound delivered. This will take place at each clinical site, by the ultrasound machine suppliers, and takes approximately one day for all the machines at one site. Previous studies have indicated that there are differences between the 'nominal' dose and that actually delivered by the machines.²² Some of this is apparent at machine delivery, and some is due to drift or step-changes in output.²³ This will allow us to determine whether the ultrasound machine output has changed over the duration of the trial. Should significant change in ultrasound output occur, then a per protocol analysis will exclude patients who have not received the prescribed dose of ultrasound ($\pm 20\%$). Each ultrasound machine will be numbered so that patients who have received treatment from individual machines can be identified. This check will take place when a site has been recruiting for 3 months and 3 monthly thereafter.

8 Ethical arrangements

8.1 Adverse effects and anticipated benefits to participants and society

Given the chronic nature of venous leg ulceration, the identification of an intervention that increases healing rates at a reasonable cost would be highly beneficial to leg ulcer patients and the NHS. The known adverse effects associated with ultrasound are pain, erythema, allergy to conducting jelly, and pinhead bleeding in the skin around the ulcer. In previous trials these were reported in 5%–10% of patients, and none were classed as serious adverse events. The local nurse, using a proforma, will routinely record any adverse events associated with any of the trial treatments during the trial. Training will emphasise the need to record and report adverse effects.

8.2 Informing trial participants of possible benefits and risks of intervention

All trial participants will be provided with a patient information sheet prior to their giving consent. The information sheet will outline fully the potential benefits and risks of being involved in the trial. This information sheet will meet all the requirements of the local ethics committees.

8.3 Informed consent

Maintenance of confidentiality and compliance with the UK Data Protection Acts will be emphasised to all study participants. Participation in the study will be entirely voluntary and written consent will be sought. All data will be treated with the strictest confidence. A variety of ethnic groups are likely to be involved in this trial. Contact with individuals from all cultures will be handled with suitable care. We will translate information sheets/consent forms and use local translators to negotiate consent in sites where a significant proportion of people with ulcers speak languages other than English (e.g. Leeds/Bradford).

8.4 Proposed action if informed consent is not possible

One of the inclusion criteria is that people are able to provide written informed consent to participate in the study. If a clinician does not feel that the potential participant meets this requirement (e.g. if they have a diagnosis of cognitive impairment) then they would not be eligible for inclusion in the study.

8.5 Proposed time period for retention of trial documents

All paper copies of patient information will be kept in a locked room at the University of York with identifying information kept separate from the coded data collection forms. Computerised data will be password protected on a computer at the University of York. The Trials Unit will retain all study treatment disposition records in a secure data archive for 5 years from the end of the trial.

9 Statistical considerations

9.1 Proposed sample size

The majority of data on ulcer healing is presented as proportion of ulcers healed at 12 or 24 weeks but the choice of an arbitrary end point fails to capture the time course of healing and can be misleading. We will therefore base the sample size on median time to healing. There is evidence from audits of healing rates, and a prognostic study of ulcer healing, that 'hard-to-heal' ulcers take approximately twice as long to heal as new/small ulcers when treated with four-layer compression. Lambourne *et al.*⁸ and Vowden *et al.*⁹ found that 60% of ulcers > 10 cm², and 60% of ulcers of > 6 months duration (treated with four-layer compression) healed in 24 weeks (168 days). This represents a median time to heal of 15–22 weeks (estimated from survival curve). Our sample will include some smaller ulcers, but importantly it will include people with both high ulcer duration and large area (of whom between 13% and 37% heal at 24 weeks with high compression),⁷ and therefore, overall we have estimated that 50% of ulcers in the standard care group will heal within 22 weeks.

We estimate that clinicians and patients would value a reduction in healing time of 7 weeks (a 32% reduction in healing time from 22 weeks to 15 weeks) and have based our sample size calculation on this premise. To detect a difference in median healing time of 7 weeks (from 22 weeks to 15 weeks), we require 306 patients in total. When we allow for 10% attrition, this brings the total sample size to 336. A 10% dropout rate has been allowed for in this trial, although VenUS I had no attrition in primary outcome data. Based on this figure and current caseloads, it is estimated that it will take 15 months to recruit sufficient people for the trial, with each area expected to recruit around 50 patients – three patients per month (22 patients total per month). We have allowed 18 months overall for recruitment.

A sample size of 336 patients also gives us 80% power to detect an 8-week reduction in median time to healing from 24 weeks and 90% power to detect this difference from 26 weeks, see Table 2.

9.2 Recruitment rate

Experience from VenUS I has informed the likely recruitment rate. In VenUS I, Cumbria, Leeds and Southport each recruited 36–60 patients per year with venous ulcers (sustained over 1–2 years). A smaller 'pool' of people will be eligible for VenUS III as we are excluding people who have small, non-chronic ulcers. In VenUS I, 60% of participants had an ulcer that was both 'small' and 'new'; these would not be eligible for inclusion in this trial. We anticipate that patient and clinician interest will be greater for this trial as it offers an opportunity to improve healing rates in a group of patients in whom standard therapy has a low success rate (and centres report

TABLE 2 Sample size for a two-arm trial; alpha 0.05, survival analysis (no allowance for dropout)

Median time to heal in standard care	Median time to heal in Rx	Difference in weeks	Difference in days (% of baseline)	Total sample size for 80% power	Total sample size for 90% power
22 weeks	14.5	7.5	52 (34)	198	258
22 weeks	15.0	7.0	47 (30)	228	306
22 weeks	15.5	6.5	45 (29)	274	366
22 weeks	16.0	6.0	42 (27)	332	444
24 weeks	15.5	8.5	59 (35)	344	460
24 weeks	16.0	8.0	56 (33)	288	384
24 weeks	16.5	7.5	52 (31)	242	326
26 weeks	18.0	8.0	56 (31)	256	344
26 weeks	19.0	7.0	49 (27)	354	476
26 weeks	20.0	6.0	42 (23)	510	682

Calculated using POWER AND PRECISION sample size program, Version 2 (Biostat, Englewood, NJ) – 52 week accrual and 52 week additional follow-up.

increasing numbers of ‘hard-to-heal’ ulcers). This suggests that each centre could be confidently expected to recruit *at least* 40% of the patients for VenUS III, which they recruited for VenUS I. The contraindications for ultrasound therapy are unlikely to exclude many patients (few have ankle prostheses, or local cancer) and people with an ulcer infection can be recruited into the trial once the infection resolves.

We have also considered that during the proposed recruitment phase for VenUS III we are also co-ordinating a concurrent HTA funded trial (VenUS II – larval therapy) which is recruiting people with venous or arterial/venous ulcers in whom at least 25% of the ulcer is covered in slough. This is likely to reduce, by a small proportion, the number of people available for the ultrasound trial but we anticipate that the benefits of having a CRN already in place in the sites, identifying people eligible for the larval therapy or ultrasound trials, will increase the efficiency of the recruitment process and reduce some of the start-up costs. Furthermore, at the start of recruitment to the ultrasound trial there will be a cohort of patients with ulcers who did not wish to take part in the larval therapy trial who may be eligible for inclusion in this trial. Throughput data from the sites not involved in VenUS I (these were Cumbria, Southport and Leeds) confirms their ability recruit patients into the trial. Hull has around 140 new ulcers per year, Altnagelvin has 150 new patients per year, and Bradford has more than 300 new ulcers per year; the majority of which are venous.

We will assess recruitment problems by having regular monitoring of recruitment to identify problems, such as needing to extend the catchment area served by a recruitment centre and having monthly newsletters to CRNs. We will also invite CRNs to update meetings at the Trials Unit to encourage sharing of good practice and engender esprit de corps.

In order to recruit 336 patients over 18 months, we require 19 patients per month across all sites. For sites with CRN staffing of 2 days per week this equates to three patients per month, and for sites with 1 day per week, 1.5 patients per month.

10 Statistical analysis

10.1.1 Data management

All data from the trial will be collected using paper-based forms (case record forms, CRFs). Research nurses will be responsible for ensuring the completeness and reliability of the data from their site, and then for conveying paper records to the University of York Trials Unit. Data from CRFs will then be entered into a master database for the trial using optical scanning techniques.

10.1.2 Analysis of clinical data

Data on baseline demographic characteristics such as gender, age, ulcer duration and size, and clinical signs of infection will be summarised and descriptive summary statistics provided. All tests for significance will be based on two-tailed tests. Simple incidence rates, relative risks and 95% CIs will be obtained for all binary variables in the first instance, with subsequent multiple logistic regression analysis conducted if important confounding is shown to exist. The effectiveness of the interventions on time-to-event outcomes, such as time to healing, will be analysed using Kaplan–Meier curves and log-rank test to compare the differences between the two groups. Cox proportional hazards regression analysis will be used to assess time-to-event data, taking into account known covariates. The proportionality assumption will be checked using standard graphical techniques and interval censoring will be employed where appropriate (e.g. analysis of time to healing where the exact day of healing is not known). The initial comparison will be between the survival (time to healing) curves for the two groups (ultrasound and standard care). Sensitivity analysis will be carried out to determine the effect of missing data from patients that are lost to follow-up. All randomised participants who receive study treatment will be included in an analysis of the tolerability of treatment. The numbers of participants discontinuing treatment prematurely for any reason will be summarised by treatment group and by reasons for discontinuation. The incidence of all suspected adverse treatment reactions will be summarised by treatment group.

A per protocol analysis will be undertaken in which only patients receiving ultrasound from machines which were found to be delivering 80%–120% of the prescribed ultrasound dose, will be included.

10.1.3 Analysis of economic and quality of life data

Cost and clinical health benefits associated with the different dressings being compared will be combined in two different types of economic evaluation analysis. First, a simple marginal cost-effectiveness ratio of cost per ulcer free days will be estimated. Second, a cost per quality-adjusted life-year (QALY) gained will also be calculated. The perspective of the economic analyses will be that of the UK National Health Service. Health benefits will be measured in terms of both Kaplan–Meier estimates of the mean time to healing after 12 months per trial arm, and QALYs. The EQ-5D will be used to elicit patient utility values at different points in time.²⁵ These utility values will then be used to ‘quality adjust’ each patient’s survival time (if the patient dies, a zero value is applied after the point of death). QALYs will be calculated for each patient using the area under the curve of the patient’s utility scores versus time, QALYs will also be adjusted for any imbalances in the EQ-5D scores between groups at baseline. Information regarding patient’s resource use may be truncated at any point in time before the end of the study, i.e. cost data are naturally censored. Consequently, the Lin *et al.* method²⁶ will be used to estimate mean total treatment cost for each treatment arm. Given the likely skewness of the distribution of the cost data, bootstrapping techniques will be used to estimate a 95% CI of the average mean cost difference between trial arms.

11 Supervision of trial

This trial will be run according to the Medical Research Council (UK) Good Clinical Practice Guidelines.³⁹ A Study Management Committee will be established to oversee the conduct of this trial. The committee will consist of the study co-ordinator and data management staff, the principal investigator and the trial statistician. Meetings to discuss the data will be held by on a quarterly basis. The committee will provide 6 monthly reports of the progress, or completion, termination or discontinuation of the study to the local ethics committees.

A Trial Steering Committee consisting of the principal investigator of the study, an independent chair and at least two other independent members will be established to discuss on a 6 monthly basis progress with the trial. The trial co-ordinator and the study statistician will attend the meetings as required.

A Data Safety and Monitoring Committee made up of experts independent from the principal investigators and host institutions will monitor the study data. This committee will monitor the data after the first 100 patients. This committee will monitor the progress of the trial, adherence to the trial protocol, and the consideration of any new information and will focus on maintaining the dignity, rights, safety and well being of all study participants. The study data will be provided to the committee members in the form of a data report, including information on any adverse events.

12 Project timetable and milestones

The trial will take 3 years to complete, with 18 months recruitment and 12 months follow-up.

TABLE 3 Project time line

Prior to trial start (not funded)	Start date to be arranged	Notification from HTA/amendment of study protocol if required/investigators meeting for protocol and data collection tools sign-off
3 months prior to trial start		Apply for MREC/advertise trial co-ordination and research nurse posts
1–2 months prior to trial start		Interview and appoint trial co-ordination and research nurse posts
Uplift grant		Apply for LREC. Trial co-ordinator will develop study materials and training materials for CRNs
Months 1–2		
Months 3–20		CRNs start in post. Train CRNs then local nurses in ultrasound use / trial documentation. Commence recruitment and randomisation of participants, ongoing data entry and cleaning
Month 8		112 patients recruited
Month 14		224 patients recruited
Month 20		336 patients recruited
Months 21–32		Complete follow-up of all patients; ongoing data entry and cleaning; drafting final report
Months 33–36		Analysis and final draft report

13 Staff roles

Trial Co-ordinator. This person will be responsible for the day to day running of the trial. She or he will help recruit CRNs in each site, provide training (with CRNs) to all community and hospital nurses involved in recruiting to the trial; draft 6 monthly reports to HTA; compile newsletters for clinical sites; liaise with Local Research Ethics Committee (LREC) and MREC regarding study progress; visit trial sites for source data verification; support CRNs in achieving their recruitment targets and ensure the quality of their work; raise the profile of the trial by writing articles describing the study for professional journals; submit the study to the National Research Register and Clinical Trials Registers, and contributing to the drafting of the final report.

Secretary (UK). This person will be the initial point of contact for CRNs, collaborators and all external queries regarding the trial. She or he will undertake general trial-related secretarial duties including submissions to Ethics and Clinical Governance committees, case record filing, organisation of study days and meetings; provision of data collection tools to sites; arrangement of Trial Management and Steering Group meetings (including preparation of agendas, minutes), compilation of final draft report.

Clinical Research Nurses. At each clinical site a CRN will identify patients potentially eligible for participation in the trial; approach potential trial participants and invite them to participate; support local nurses in recruiting their patients into the trial, undertake initial clinical assessments; audit ultrasound treatments locally; undertake follow-up assessments; participate in trial-related training of community nurses; support local community nurses in trial participation; maintain a high profile for the trial locally; check the completeness and accuracy of all data forms; return completed forms to York.

Data manager. This person will be responsible for data entry and cleaning of all UK-derived clinical, economics and QoL. She or he will be responsible for generating reminders for nurses/patients to complete the QoL data (every 3 months), will receive and log all completed clinical, QoL and economic data, prepare recruitment and data completion reports for the Trial Steering Committee, run data checks, and preparing summary reports for the final report.

Statistician. This person will conduct all analyses of the clinical data under supervision of Professor Bland.

Principal investigator. The named lead investigator has overall responsibility within the team of researchers for the design, conduct and reporting of the study.

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15 References

1. Callam MJ, Harper DR, Dale JJ, Ruckley CV, Prescott RJ. A controlled trial of weekly ultrasound therapy in chronic leg ulceration. *Lancet* 1987;**2**(8552):204–6.
2. Roe B, Cullum N, Hamer C. Patients' perceptions of chronic leg ulceration. In Cullum NA, Roe BH, editors. *Leg ulcers: nursing management*. London: Balliere Tindall; 1995. pp. 125–34.
3. Dale JJ, Callam MJ, Ruckley CV, Harper DR, Berrey PN. Chronic ulcers of the leg: a study of prevalence in a Scottish community. *Health Bull (Edinb)* 1983;**41**(6):311–14.
4. Laing W. *Chronic venous diseases of the leg*. London: Office of Health Economics; 1992. pp. 1–44.

5. Cullum N, Fletcher AW, Nelson EA, Sheldon TA. Compression bandages and stockings in the treatment of venous ulcers (Cochrane Review). *Cochrane Database Syst Rev* Oxford: Update Software; 2000.
6. Iglesias C, Nelson EA, Cullum NA, Torgerson DJ, for the VenUS Team. The VenUS I trial: a randomised comparison of 4-layer and short-stretch bandages for the treatment of venous leg ulcers. *Health Technol Assess* 2004;**8**(29).
7. Margolis DJ, Berlin JA, Strom BL. Which venous leg ulcers will heal with limb compression bandages? *Am J Med* 2000;**109**:15–19.
8. Lambourne LA, Moffatt CJ, Jones AC, Dorman MC, Franks PJ. Clinical audit and effective change in leg ulcer services. *J Wound Care* 1996;**5**(8):348–51.
9. Vowden KR, Barker A, Vowden P. Leg ulcer management in a nurse-led, hospital-based clinic. *J Wound Care* 1997;**6**(5):233–6.
10. Baker KG, Robertson VJ, Duck FA. A review of therapeutic ultrasound: biophysical effects. *Phys Ther* 2001;**81**(7):1351–8.
11. Low J, Reed A. *Electrotherapy explained: principles and practice*. Oxford, England: Butterworth Heinemann; 1994.
12. ter Haar G. Basic physics of therapeutic ultrasound. *Physiotherapy* 1987;**73**:110–3.
13. Dyson M. Role of ultrasound in wound healing. In McCulloch JM, Kloth LC, Fudar JA, editors. *Wound healing: alternatives in management*. 2nd edn. FA Davis, Philadelphia, 1995. pp. 318–46.
14. Draper DO, Sunderland S, Kirkendall DT, *et al*. A comparison of temperature rise in human calf muscle following applications of underwater and topical gel ultrasound. *J Orthop Sports Phys Ther* 1993;**17**:247–51.
15. IEC 60601-2-5: Medical Electrical Equipment – Part 2-5: Particular requirements for the safety of ultrasonic physiotherapy equipment International Electrotechnical Commission, Geneva, Switzerland, (Ed 2.0) 2000.
16. IEC 61689: Ultrasonics – Physiotherapy Systems – Performance requirements and methods of measurement in the frequency range 0.5 to 5 MHz International Electrotechnical Commission, Geneva, Switzerland, 1996.
17. Enraf Nonius. *Ultrasound therapy*. Delft: Enraf-Nonius BV; 1995.
18. Flemming K, Cullum N. Therapeutic ultrasound for venous leg ulcers. *Cochrane Database Syst Rev* 2000;**4**:CD001180.
19. Swist-Chmielewska D, Franek A, Brzezinska-Wcislo L, Blaszczyk E, Polak A, Krol P. Experimental selection of best physical and application parameters of ultrasound in the treatment of venous crural ulceration. *Pol Merk Lek* 2002;**12**(72):500–5.
20. RCN Institute, Centre for Evidence Based Nursing, University of York and School of Nursing Midwifery and Health Visiting, University of Manchester. *Clinical practice guidelines. The management of patients with venous leg ulcers. Recommendations for assessment, compression therapy, cleansing, debridement, dressing, contact sensitivity, training/education and quality assurance*. London: Royal College of Nursing Institute; 1998.
21. Margolis DJ, Berlin JA, Strom BL. Risk factors associated with the failure of a venous leg ulcer to heal. *Arch Dermatol* 1999;**135**(8):920–6.
22. ter Riet G. Problems in the conduct of a randomised controlled trial. *J Wound Care* 1998;**7**(5):259–62.

23. Pye S. Ultrasound therapy equipment: does it perform? *Physiotherapy* 1996;**78**:263–7.
24. Gardner SE, Frantz RA, Troia C, Eastman S, MacDonald M, Buresh K, *et al.* A tool to assess clinical signs and symptoms of localized infection in chronic wounds: development and reliability. *Ostomy Wound Manage* 2001;**47**(1):40–7.
25. Kind P. Quality of Life and Pharmacoeconomics in Clinical Trials. In Spilker B (editor). *The EuroQoL instrument: an index of health-related quality of life*. Philadelphia: Lippincott-Raven; 1996.
26. Lin DY, Feuer EJ, Etzioni R, Wax Y. Estimating medical costs from incomplete follow-up data. *Biometrics* 1997;**53**:419–34.
27. Vowden K, Goulding V, Vowden P. Hand-held Doppler assessment for peripheral arterial disease. *J Wound Care* 1996;**5**(3):125–7.
28. Simon D, Freak L, Williams I, McCollum C. Progression of arterial disease in patients with healed venous ulcers. *J Wound Care* 1994;**3**(4):179–80.
29. Kantor J, Margolis DJ. A multicentre study of percentage change in venous leg ulcer area as a prognostic index of healing at 24 weeks. *Br J Dermatol* 2000;**142**(5):960–4.
30. Etris MB, Pribble J, LaBrecque J. Evaluation of two wound measurement methods in a multi-center, controlled study. *Ostomy Wound Manage* 1994;**40**(7):44–8.
31. Ware JE, Kosinski N, Keller SD. The 12-Item Short-Form Health Survey (SF-12): construction of scales and preliminary tests of reliability and validity. *Medical Care* 1996;**34**:220–33.
32. Jenkinson C, Layte R, Jenkinson D, Lawrence K, Peterson S, Paice C, *et al.* A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? *J Public Health Med* 1997;**19**:179–96.
33. Iglesias CP, Birks YF, Torgerson DJ. Improving the measurement of quality of life in older people: the York SF-12. *QJM Monthly Journal of the Association of Physicians* 2001;**94**(12): 695–8.
34. Walker NK. *Epidemiological studies of leg ulcers in Auckland, New Zealand*. PhD thesis. Auckland: University of Auckland; 2000.
35. Kind P, Hardman G, Macran S. *UK population norms for EQ-5D*. Centre for Health Economics discussion paper 172. York: Centre for Health Economics, University of York; 1999.
36. European Committee for Standardisation (CEN). *Clinical Investigation of Medical Devices for Human Subjects EN 540*. Brussels: European Committee for Standardization; 1993.
37. Edwards P, Roberts I, Clarke M, DiGuseppi C, Pratap S, Wentz R. Increasing response rates to postal questionnaires: systematic review. *BMJ* 2002;**324**(7347):1183.
38. Medical Research Council. *Guidelines for good clinical practice in clinical trials*. London: Medical Research Council; 1998.

Appendix 2

Regulatory approvals

The MREC approval was obtained for the study from the York Research Ethics Committee on 4 February 2005. The LRECs were also approached in each recruitment area prior to recruitment as were the relevant Research and Development departments. Approval was given at the following meetings.

Site	PCT/trust	Site	LREC	Approved	Research and development approval
Western Trust	Althagevin Health and Social Services Trust	Health and Social Care REC 1		26 April 2005	5 December 2005
Bolton	Bolton PCT/Bolton Hospitals NHS Trust	Bolton REC		19 August 2005	1 November 2005
Bradford	Bradford Teaching Hospitals NHS Trust	Bradford REC		11 February 2005	29 June 2005
Cumbria	West Cumberland Hospital	Cumbria and Lancashire A		26 April 2005	4 May 2005
Dunfermline	NHS Fife	Fife and Forth Valley REC		14 March 2006	4 May 2006
Hull	Hull and East Yorkshire Hospitals NHS Trust	Hull and East Riding REC		14 March 2005	15 May 2006
South Essex	Castle Point and Rochford PCT; Southend on Sea PCT	Essex 2 REC		4 May 2006	7 July 2006
Leeds Community	Leeds PCTs Research Consortium	Leeds (East) REC		27 April 2005	6 October 2005
Scarborough	Scarborough, Whitby and Ryedale PCT	York REC		26 July 2005	20 August 2005
Nottingham	Nottinghamshire County Teaching PCT; Nottingham City PCT; Gedling PCT; Rushcliffe PCT; Broxtowe and Hucknall PCT	Nottingham REC 1		17 May 2006	10 July 2006
Birmingham	University Hospital Birmingham NHS Foundation Trust	South Birmingham REC		19 September 2006	17 October 2006
Dublin	The Adelaide and Meath Hospital, Dublin	St. James's Hospital/Adelaide and Meath Hospital incorporating the National Children's Hospital		30 November 2006	Not required at time

PCT, primary care trust; REC, research ethics committee.
Approval was gained at two additional sites, but neither was ever able to start recruitment.

Appendix 3

Details of the study sites

Site	Site organisation and recruitment dates
Bolton	Outpatient leg ulcer clinics (recruited first patient March 2006; last patient September 2008)
Scarborough	Leg ulcer clinics/community tissue viability service/district nurse teams (recruited first patient March 2006; last patient December 2008)
Cumbria	Outpatient leg ulcer clinics (recruited first patient May 2006; last patient November 2007)
Western Trust	Outpatient leg ulcer clinic/community service (recruited first patient March 2006; last patient October 2008)
Leeds Community	Community tissue viability service (recruited first patient April 2006; last patient December 2008)
Hull	Outpatient leg ulcer clinics (recruited first patient February 2007; last patient December 2008)
Dunfermline	Outpatient leg ulcer clinics (recruited first patient February 2007; last patient July 2008)
Nottingham	Outpatient leg ulcer clinics/community service (recruited first patient October 2006; last patient December 2008)
South Essex	Leg ulcer clinics/leg ulcer clubs (recruited first patient October 2006; last patient November 2006)
Birmingham	Outpatient leg ulcer clinics (recruited first patient January 2007; last patient September 2008)
Bradford	Outpatient leg ulcer clinics (recruited first patient November 2006; last patient December 2008)
Dublin	Outpatient wound clinics (recruited first patient January 2007; last patient February 2007)

Appendix 4

Information sheet for patients

Patient Information Sheet

Local headed paper

Please read this document carefully.

We would like to invite you to take part in this study of **ultrasound** therapy used in the treatment of leg ulcers. Ultrasound therapy is the application of inaudible sound energy to help with healing.

Leg ulcers are common, costly to the NHS and can be very distressing for patients. There are a range of treatments currently being used to do this, for example, wound dressings and bandages. The use of compression bandages is very effective however, this kind of treatment can work quite slowly, and it is thought that ultrasound therapy may speed up the rate of healing.

Ultrasound therapy involves the use of sound waves to the skin around the ulcer. A watery jelly is applied to the skin so that the sound waves can travel into the skin at the edge of the ulcer.

The purpose of this study is to find out if adding ultrasound therapy to the best possible care (firm compression bandages applied by your nurse) helps in healing leg ulcers. We are interested in how quickly the ulcers heal, and also in your opinion about the treatment you receive. In order to compare the treatments we need to treat approximately 168 patients with the ultrasound therapy and bandages, and 168 patients with bandages. If you agree to take part in this study you will be allocated to one of these two treatments. The decision regarding which treatment you will receive will be made after you agree to take part. The choice of treatment will be determined at random, that is we cannot predict which treatment you will receive. You will have an equal chance of receiving each treatment, in the same way that tossing a coin gives an equal chance of getting 'heads' or 'tails'.

Your leg ulcer dressings will be carried out, as normal, by your community nurse or clinic staff. The ulcer will be traced and photographed at the start of the study and then regularly to see if the ulcer is reducing in size. The study will last for 12 months, but you would receive ultrasound for a maximum of 12 weeks; if your ulcer heals in the first 12 weeks of treatment, you will only receive ultrasound therapy up to the date of healing. During the trial you will be asked to complete five short questionnaires. We envisage that each of these questionnaires will take less than 15 minutes to complete. We will continue to send you questionnaires about your leg and how it affects you, even if your ulcer has completely healed. We do not anticipate that you will have to see the nurse or attend your clinic more frequently than would normally be required and we will therefore not be able to pay any travel expenses incurred.

Why do the study?

Ultrasound therapy given once a week, for 5 to 10 minutes, in addition to bandages, may heal more ulcers than using bandages alone. It is therefore important to carry out this study so that patients with leg ulcers can be provided with the most appropriate and effective care. We are also interested in how you feel having the leg ulcer treatment so that nurses, doctors and patients can

make future decisions about which treatments are comfortable. Without this information patients may receive inefficient care.

Can I change my mind later?

Participation in this study is entirely voluntary. You can change your mind at any time. Your future care and treatment will not be influenced by your decision to take part or not. If you do agree to take part in this study and decide at a later time to withdraw then you are free to do so at any time without influencing your future care or treatment.

Are there any side-effects from the ultrasound therapy?

There may be some tingling pain around the ulcer edge from the ultrasound therapy, or redness. A small proportion of people – fewer than 1 in 10 – have reported pinhead bleeding in the skin around the ulcer. We do not anticipate that you will be harmed by being on this trial. Should this occur, however, normal NHS negligence procedures will apply. If you have any problems you should contact your community nurse or clinic nurse. The name of a contact nurse and telephone number where they can be reached is provided below.

What do I do now?

If you are interested in taking part please tell your nurse. They will give you a consent form to sign and a questionnaire to be completed.

Where can I get more information about the study?

If you do not understand anything on this information sheet or would like further information please contact your local research nurse on the telephone number below.

Local Nurse:

Telephone number:

Local Investigator:

Telephone number:

Research Co-ordinator:


Telephone number:

Address:

Thank you for taking the time to read this information sheet

Appendix 5

Data collection forms

<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>Date</p> <table style="border-collapse: collapse; margin: 0 auto;"> <tr> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="font-size: 8px; margin: 0 5px;">/</td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="font-size: 8px; margin: 0 5px;">/</td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> </tr> <tr> <td style="font-size: 8px; margin-top: 2px;">day</td> <td></td> <td></td> <td style="font-size: 8px; margin-top: 2px;">month</td> <td></td> <td></td> <td style="font-size: 8px; margin-top: 2px;">year</td> <td></td> <td></td> <td></td> </tr> </table> </div> <div style="text-align: center;">  </div> </div>			/			/					day			month			year									
		/			/																					
day			month			year																				
<p>VenUS III: Ultrasound Trial - Pre-trial Screening Form (April 2006)</p>																										
<p>Centre: <input style="width: 250px;" type="text"/> Patient Sex: Male <input type="checkbox"/> Female <input type="checkbox"/></p>																										
<p>Patient's DoB: <input style="width: 20px;" type="text"/> / <input style="width: 20px;" type="text"/> / <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/> <input style="width: 20px;" type="text"/></p> <p style="text-align: center; font-size: 8px;">day month year</p>																										
<p>Current compression level: High <input type="checkbox"/> Moderate/Low <input type="checkbox"/> None <input type="checkbox"/></p>																										
<p>Does the patient's leg ulcer have more than 25% slough? Yes <input type="checkbox"/> No <input type="checkbox"/></p>																										
<p>If Yes, please consider the patient for inclusion in the VenUSII larval therapy trial, if available in your centre.</p>																										
<p>The following are exclusion criteria for the VenUSIII Ultrasound trial: Please Cross ALL that apply</p> <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 80%;"></th> <th style="text-align: right; width: 20%; font-weight: normal;">Yes</th> </tr> </thead> <tbody> <tr><td>1. Patient has been in VenUS III ultrasound trial previously</td><td style="text-align: right;"><input type="checkbox"/></td></tr> <tr><td>2. Patient has one or more of the contraindications to Ultrasound <i>that are listed overleaf.</i> (Please indicate which by crossing the relevant box overleaf)</td><td style="text-align: right;"><input type="checkbox"/></td></tr> <tr><td>3. Patient is a woman of child bearing potential, or pregnant or breastfeeding</td><td style="text-align: right;"><input type="checkbox"/></td></tr> <tr><td>4. Patient is currently in a trial evaluating other therapies for leg ulcers (except for 6 months post-recruitment into the VenUSII larval therapy trial)</td><td style="text-align: right;"><input type="checkbox"/></td></tr> <tr><td>5. Patient is allergic to ultrasound transmission gel</td><td style="text-align: right;"><input type="checkbox"/></td></tr> <tr><td>6. ABPI is less than 0.8 (measured within the last 3 months)</td><td style="text-align: right;"><input type="checkbox"/></td></tr> <tr><td>7. Patient's leg ulcer is equal to or less than 5cm² in area and less than 6 months duration</td><td style="text-align: right;"><input type="checkbox"/></td></tr> <tr><td>8. Patient will not consider ultrasound therapy</td><td style="text-align: right;"><input type="checkbox"/></td></tr> <tr><td>9. Patient has uncontrolled diabetes (HbA_{1c} > 10% measured within the last 3 months)</td><td style="text-align: right;"><input type="checkbox"/></td></tr> <tr><td>10. Patient unwilling to give informed consent</td><td style="text-align: right;"><input type="checkbox"/></td></tr> <tr><td>11. Patient unable to give informed consent</td><td style="text-align: right;"><input type="checkbox"/></td></tr> <tr><td>12. Patient is under 18 years of age</td><td style="text-align: right;"><input type="checkbox"/></td></tr> </tbody> </table>		Yes	1. Patient has been in VenUS III ultrasound trial previously	<input type="checkbox"/>	2. Patient has one or more of the contraindications to Ultrasound <i>that are listed overleaf.</i> (Please indicate which by crossing the relevant box overleaf)	<input type="checkbox"/>	3. Patient is a woman of child bearing potential, or pregnant or breastfeeding	<input type="checkbox"/>	4. Patient is currently in a trial evaluating other therapies for leg ulcers (except for 6 months post-recruitment into the VenUSII larval therapy trial)	<input type="checkbox"/>	5. Patient is allergic to ultrasound transmission gel	<input type="checkbox"/>	6. ABPI is less than 0.8 (measured within the last 3 months)	<input type="checkbox"/>	7. Patient's leg ulcer is equal to or less than 5cm ² in area and less than 6 months duration	<input type="checkbox"/>	8. Patient will not consider ultrasound therapy	<input type="checkbox"/>	9. Patient has uncontrolled diabetes (HbA _{1c} > 10% measured within the last 3 months)	<input type="checkbox"/>	10. Patient unwilling to give informed consent	<input type="checkbox"/>	11. Patient unable to give informed consent	<input type="checkbox"/>	12. Patient is under 18 years of age	<input type="checkbox"/>
	Yes																									
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<p style="text-align: center; font-size: 8px;">If you have put an 'X' in any box, this means the patient is NOT ELIGIBLE to enter the trial. If this is the case please RETURN THIS FORM to your local research nurse.</p>																										
<p>If the patient is ELIGIBLE to enter the trial, please give them the patient information sheet. Arrange to see them after at least 24 hours (you may wish to see them at your next scheduled appointment rather than arranging a special visit).</p>																										
<p>Please now give the patient information sheet to the patient.</p>																										
<p>Nurse's name <input style="width: 200px;" type="text"/> Signature <input style="width: 150px;" type="text"/></p>																										
<p style="font-size: 8px;">5958287868 1</p>																										

Recognised contraindications to Ultrasound treatment are (on the leg to be treated):

Please cross relevant
contraindication

- Ankle or knee prosthesis
- Metal anywhere in the foot or leg (e.g. pin or plate; shrapnel)
- Suspected or confirmed local cancer/metastatic disease
- Suspected thrombophlebitis (*please reconsider patient for trial once this has resolved*)
- Active cellulitis (*please reconsider patient for trial once this has resolved*)
- Obvious ulcer infection (*please reconsider patient for trial once this has resolved*)
- Other

If Other please specify _____

Date Form Completed


		/			/				
<i>day</i>			<i>month</i>			<i>year</i>			

VenUS III: Ultrasound Trial -Patient Record Form

BEFORE completing this form please ensure that the patient has signed the consent form indicating their willingness to take part in the trial

Date informed consent obtained

		/			/				
<i>day</i>			<i>month</i>			<i>year</i>			



VenUS III (Venous Ulcer Studies III - Ultrasound for venous leg ulcers)
 A multicentre randomised trial, funded by the NHS Health Technology Assessment Programme
 (International Standardised Randomised Controlled Trial No: 21175670 & EudraCT No. 2004-004911-51)

8393102444

Please follow the following checklist to confirm if the patient is eligible to enter the trial.

Please answer every question by placing a cross in the appropriate box.

1. Hard to heal criterion

Is the reference ulcer equal to or less than 5cm² in area and less than 6 months old?
(The reference ulcer is the largest ulcer in patients with more than one ulcer)

Yes

No

2. Arterial supply criterion

Is the ABPI equal to or greater than 0.8?

Yes

No

3. Consent criterion

Has the patient provided informed written consent to entering the trial?
I.e. Have they read and understood the patient information sheet and signed the patient consent form?

Yes

No

If any of the responses fall into the grey boxes then the patient is NOT ELIGIBLE for the trial

Ulcer history and initial assessment

The **reference leg** will be the leg with the largest ulcer.

1. Please indicate the leg being followed in the trial

Left Right

2. ABPI of the reference leg . Date taken / /
(e.g. 1.06 or 0.85) *day month year*

3. Total number of ulcer EPISODES on reference leg since the first episode?

4. How long is it since the patient developed the FIRST leg ulcer? years months

The reference ulcer is identified as the largest ulcer on the leg.

5. Duration of the reference ulcer? years months

6. Duration of the oldest ulcer on the reference leg? years months

7. **Mobility** (please cross one box only)

Patient walks freely

Patient walks with difficulty

Patient is immobile

8. **Ankle mobility/ trial leg** (please cross one box only)

Patient has full range of ankle motion

Patient has reduced range of ankle motion

Patient's ankle is fixed

9. Patient's Height feet inches **or** . cm

10. Patient's Weight stone lbs **or** . kgs

11. Ankle circumference (of reference leg) . cm

12. On the following diagram (Page 5), please draw and label clearly all ulcers on both legs and give each one an identification code.

Label the largest ulcer R1 (if on the right leg) or L1 (if on the left leg).

If there is more than one ulcer, order them in descending order of area, i.e. largest R1, next largest R2 etc..

Please write the identification code of the **REFERENCE ULCER** (the largest ulcer on the leg) in the box below and **CIRCLE** the reference ulcer on the following diagram of the legs.

REFERENCE ULCER IDENTIFICATION CODE (e.g. R1, L1)

Please enter the other ulcer identification codes in the boxes below.

OTHER ULCER IDENTIFICATION CODES

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

13. TRACING

Using the grids provided, please trace all the ulcers on both legs.

Please confirm you have taken tracing(s) of **ALL** ulcers on the both of the legs

Yes No

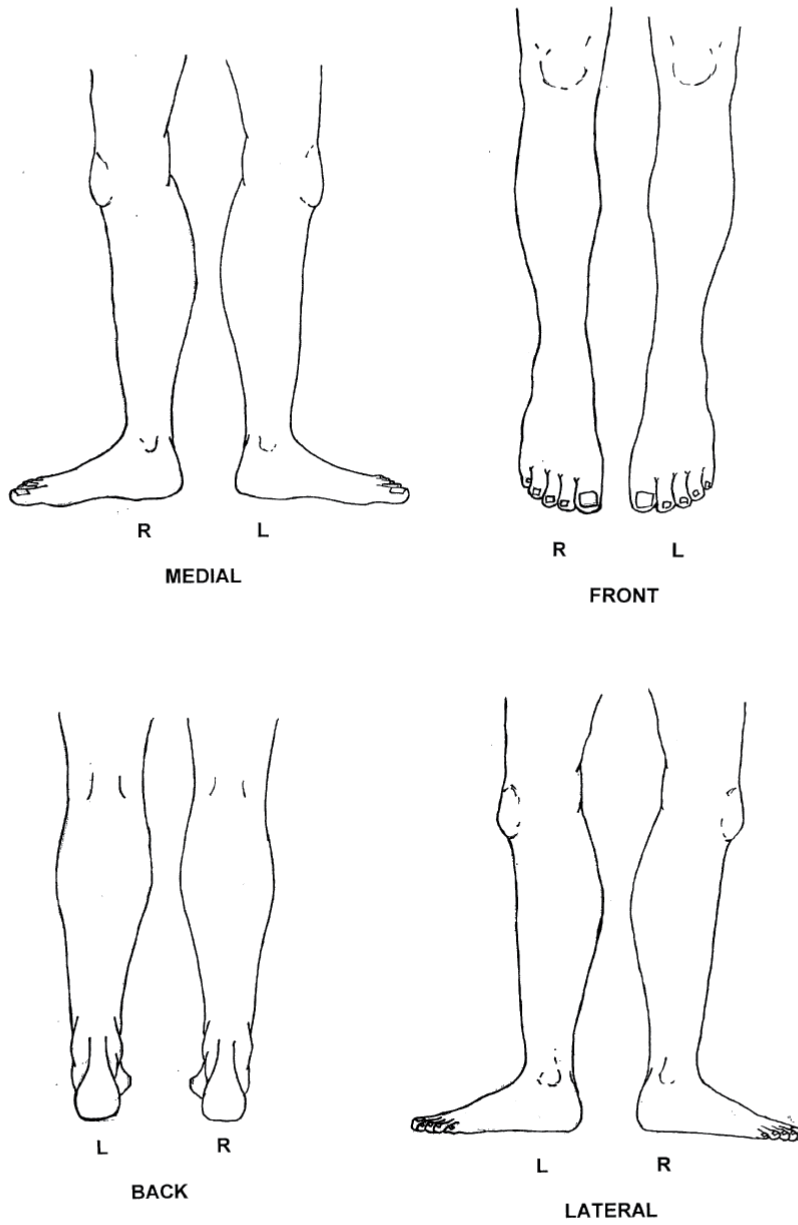
Please attach the tracings to the back of this form.

14. PHOTOGRAPH

Using the digital camera, please take a photograph of the **reference ulcer**.

Please confirm you have taken a digital photograph of the **reference ulcer**.

Yes No



15. Please ask about any pain they may have experienced from the leg ulcer(s) on the **reference leg** in the past 24 hours.

Read the instructions out to the patient on how to complete the pain analogue scale before asking the question.

Instructions for completing the scale:

Place a cross on the scale below to indicate how intense the pain you have experienced is, ranging from 'no pain' to the 'worst pain imaginable'.

Question:

What is the worst pain you have had in your leg ulcer in the last 24 hours?



Office Use Only

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16. Documentation

Has the patient completed the baseline questionnaire?

Yes	No
<input type="checkbox"/>	<input type="checkbox"/>

If **yes**, please now complete the following randomisation section and call the randomisation service in order to allocate the patient their treatment.

If **no**, please ask them to do so, and then complete the following randomisation section and call the randomisation service in order to allocate the patient their treatment.

Please complete the following section and call the randomisation service to randomise the patient.

Date								
		/			/			
<i>day</i>			<i>month</i>			<i>year</i>		

VenUS III: Ultrasound Trial Randomisation Form

Patient Details

Patient's Full Name

Patient's Address

Patient's Postcode

Patient's Telephone Nos.

Day **Eve**

Patient's Date of Birth

		/			/			
<i>day</i>			<i>month</i>			<i>year</i>		

Patient's Gender

Male Female

Trial Centre:

- | | |
|--------------------------------------|--|
| <input type="checkbox"/> Altnagelvin | <input type="checkbox"/> Hull |
| <input type="checkbox"/> Bolton | <input type="checkbox"/> Leeds Acute |
| <input type="checkbox"/> Bradford | <input type="checkbox"/> Leeds Community |
| <input type="checkbox"/> Cumbria | <input type="checkbox"/> Scarborough |
| <input type="checkbox"/> Doncaster | <input type="checkbox"/> York |
| <input type="checkbox"/> Harrogate | |
| <input type="checkbox"/> Other | |

Size of ulcer:

Equal to or less than 5cm² More than 5cm²

Ulcer duration:

Equal to or less than 6 months More than 6 months

Type of ulcer:

Venous ulcer? Yes No

Compression level:

Is this patient being treated with high compression?
(e.g. 2 or 3 or 4 layer high compression bandaging)

Yes No

Once these questions are complete, please call the randomisation service on 0800 0566682 between 08:30 and 17:30 Monday to Friday, and then complete the allocation details on the following page according to the details given by the telephonist.

THE UNIVERSITY *of York*

CONFIDENTIAL

VenUS III Ultrasound Study

Baseline Questionnaire (May 2006)

Participant ID Number

<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
----------------------	----------------------	---	----------------------	----------------------	----------------------	----------------------

This unique number will be allocated to the patient when the nurse telephones the randomisation service.

Nurse: Please enter the number in the boxes above after you have been given it by the randomisation service.

Date

<input type="text"/>	<input type="text"/>	/	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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VenUS III (Venous Ulcer Studies III - Ultrasound for venous leg ulcers)

A multicentre randomised trial, funded by the NHS Health Technology Assessment Programme
(International Standardised Randomised Controlled Trial No: 21175670 & EudraCT No. 2004-004911-51)

2270226382

This section asks about your health in general. By placing a cross in one box in each group below, please indicate which statement best describes your own health state today.

Do not cross more than one box in each group.

Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

These questions ask for your views about your health. This section will help us keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking a cross in the appropriate box. If you are unsure on how to answer a question, please give the best answer you can.

1. In general, would you say your health is:
(please cross one box only)

Excellent	Very Good	Good	Fair	Poor
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. During a typical day does **your health** limit you in **moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf? If so, how much?
(please cross one box only)

Yes, limited a lot	Yes, limited a little	No, not limited at all
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. During a typical day does **your health** limit you in climbing **several** flights of stairs? If so, how much?
(please cross one box only)

Yes, limited a lot	Yes, limited a little	No, not limited at all
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. During the **past 4 weeks**, how much of the time have you accomplished less than you would like in regular daily activities **as a result of your physical health**?
(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. During the **past 4 weeks**, how much of the time have you been limited in performing any kind of work or other regular daily activities **as a result of your physical health**?
(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6. During the **past 4 weeks**, how much of the time have you accomplished less than you would have liked in your work or any other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?
(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

7. During the **past 4 weeks**, how much of the time have you done work or other activities less carefully than usual **as a result of any emotional problems** (such as feeling depressed or anxious) ?

(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (both outside the home and housework) ?

(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

9. This question is about how you feel and how things have been with you during the **past 4 weeks**. Please give the one answer that comes closest to the way you have been feeling. How much during the **past 4 weeks** have you felt calm and peaceful ?

(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

10. This question is about how you feel and how things have been with you during the **past 4 weeks**. Please give the one answer that comes closest to the way you have been feeling. How much during the **past 4 weeks** did you have a lot of energy ?

(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

11. This question is about how you feel and how things have been with you during the **past 4 weeks**. Please give the one answer that comes closest to the way you have been feeling. How much during the **past 4 weeks** have you felt downhearted and depressed ?

(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

12. During the **past 4 weeks** how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives etc.) ?

(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please enter today's date / /

day month year

In order to accurately measure the cost of different leg ulcer treatments, we would like to know the number of times you have seen a health professional (e.g. doctor or nurse) **not** as part of this study.

1. In the **last 3 months** have you seen a doctor at your **doctor's surgery** OR seen a **doctor at home** for any reason relating to your health ?

Yes

No

If **Yes**, how many times...

have you seen a doctor at the surgery ?

have you been visited at home by a doctor ?

Were any of these visits because of your leg ulcer ?

Yes

No

If **Yes**, how many times ?

2. In the **last 3 months** have you seen a nurse at your **doctor's surgery** OR seen a **nurse at home** for any reason relating to your health ?

Yes

No

If **Yes**, how many times...

have you seen a nurse at the surgery ?

have you been visited at home by a nurse ?

Were any of these visits because of your leg ulcer ?

Yes

No

If **Yes**, how many times ?

3. In the **last 3 months** have you **been to hospital as an outpatient** for any reason relating to your health ?

Yes

No

If **Yes**, how many times...

Were any of these visits because of your leg ulcer ?

Yes

No

If **Yes**, how many times...

4. In the **last 3 months** which of the following have helped you around the house, to do the shopping etc. ?
(place a cross in the box for all of those who have helped and then enter the number of hours per week they have helped you. If you have not needed any help put a cross in the 'I have not needed any help' box)

I have not needed any help

Home help approximately how many hours per week

Relative approximately how many hours per week

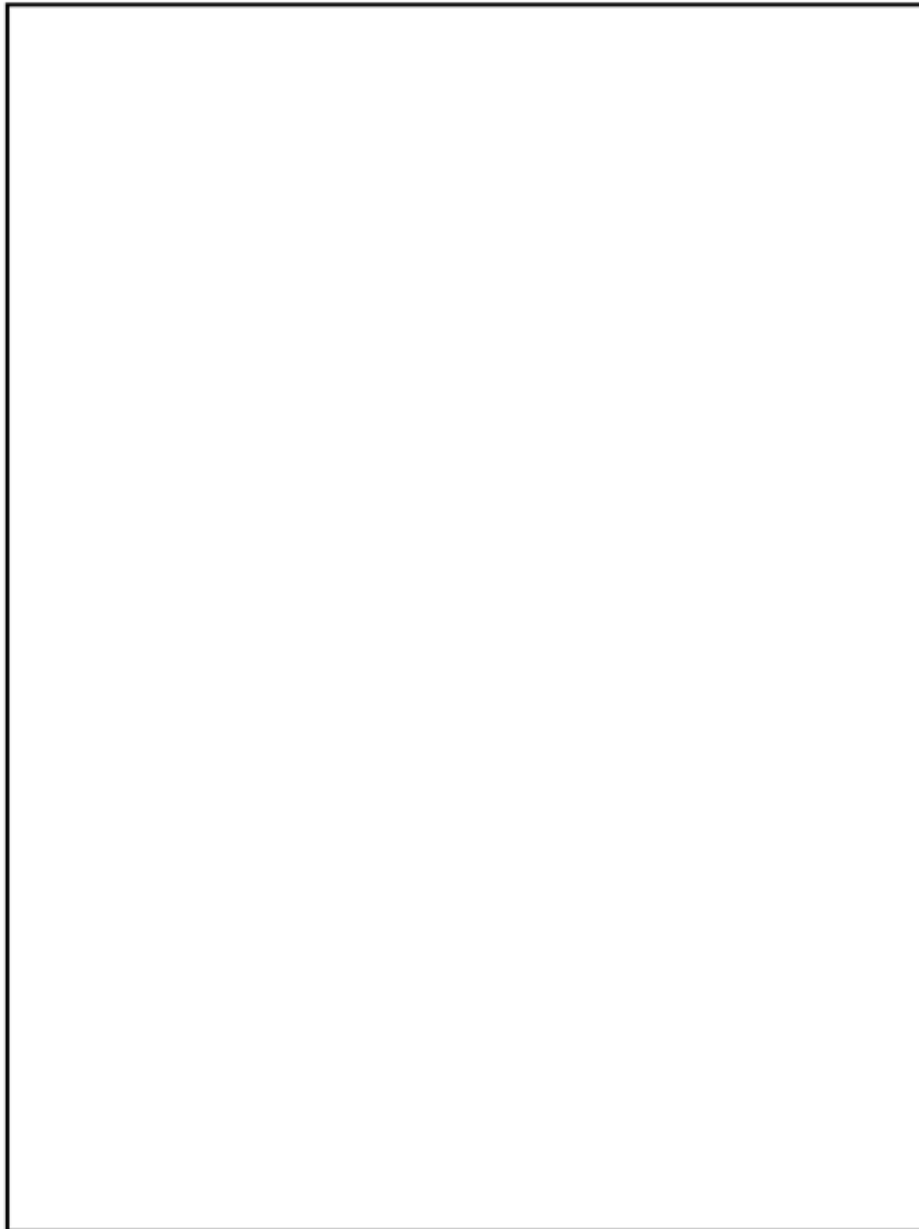
Friend/ neighbour approximately how many hours per week

Other approximately how many hours per week

If you have selected 'Other' please state relationship in box below)

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

If you have any general comments about your ulcer, the study, or this questionnaire, please write them below.





Patient Trial Number

<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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VenUS III: Ultrasound Trial

ULTRASOUND TREATMENT LOG BOOKLET (April 2006)

To be used for all patients allocated to Ultrasound DURING their 12 weeks of Ultrasound, after which the Dressing Log Booklet should be used

Booklet Number

<input type="text"/>	<input type="text"/>
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- Please complete a page in the Ultrasound Treatment Log Booklet at each visit to the patient and complete the following trial documentation at the appropriate times.
- When the Reference ulcer has healed please complete an **Ulcer Healed Form**.
- When the last ulcer has healed (i.e. the patient is ulcer free) please complete an **Ulcer Healed Form**.
- If the only ulcer on the leg has healed please also complete a **Change of Circumstances Form**.
- If there are unhealed ulcers on the leg, continue to complete the Dressing Log Booklet until all ulcers have healed - when this occurs please complete a **Change of Circumstances Form**.
- If the reference ulcer is not healed in 12 months please complete a **Change of Circumstances Form**.

Please report any patient event observed today and complete the relevant form. Please ensure you adhere to your employing Trust's adverse event procedure.

A list of possible adverse events is listed below. This is NOT an exhaustive list. If you suspect an event is serious please contact the trial manager. We would rather you err on the side of caution and report an adverse event.

Please complete a Non-Serious Adverse Event (NSAE) form for any of the following:

Pressure damage

Infection

Skin damage surrounding ulcer

New ulcer

Ulcer deterioration (Please also complete a 'Change of Circumstances Form')

Patient had experienced an adverse reaction to the ultrasound treatment or contact gel (Please also complete a 'Change of Circumstances Form')

Please complete a Serious Adverse Event (SAE) form for any of the following:

Patient has died (Please also complete a 'Change of Circumstances Form')

Patient has been admitted to hospital for more than 24 hours (Please also complete a 'Change of Circumstances Form')

Limb compromise

Life - threatening event

Persistent or significant disability/incapacity

Patient is a newly diagnosed diabetic

Please note this is not an exhaustive list, if you suspect an event is serious, please contact the Trial Manager at the York Trials Unit. We would rather you erred on the side of caution and reported an event to us.

If the patient has had any change in treatment (deviating from the protocol) please complete a 'Change of Circumstances Form'



Data collection checklist

For each visit, please complete a new page in this booklet recording the treatment applied.

Every 4 weeks from the first trial treatment (first day of treatment equals Day 0), please take a **digital photograph** of the **REFERENCE ULCER**.

Every 4 weeks from the first trial treatment (i.e. at the same time as taking the photograph of the reference ulcer), please take **tracings** of **ALL** the leg ulcers the patient has.

These key data collection times can also be seen in the "**Record of data collected for a recruited patient**" form which should be kept in the front of the patient's records.

ULTRASOUND TREATMENT LOG
PLEASE COMPLETE THIS FORM EVERY TIME A PATIENT IS SEEN BY A NURSE
FOR LEG ULCER TREATMENT IN THE FIRST 12 WEEKS AFTER TRIAL ENTRY

Date of Visit / /
day *month* *year*

Location (place a cross in one box only)

Home <input type="checkbox"/>	GP Surgery <input type="checkbox"/>
Leg ulcer clinic <input type="checkbox"/>	Leg ulcer club <input type="checkbox"/>
Nursing Home <input type="checkbox"/>	Other (specify below) <input type="checkbox"/>

Have you applied ultrasound today? (NB: once weekly) Yes No

If yes, how long was it applied for? mins

If yes, what is the machine number?

If yes, please sign to confirm you have carried out the above treatment

_____	_____
<i>(Please sign here)</i>	<i>(Please print your name here)</i>

Knitted viscose dressing (KVD) applied Yes No

Please report any change to the primary dressings and state reasons why below (please put name of primary dressing/wound contact layer/topical agent applied apart from a KVD) AND complete a 'Change of Circumstances' Form

Compression bandages applied (please cross one box only):

4 layer high compression <input type="checkbox"/>	3 layer reduced compression <input type="checkbox"/>
3 layer high compression <input type="checkbox"/>	Low compression <input type="checkbox"/>
2 layer high compression <input type="checkbox"/>	No compression <input type="checkbox"/>
Short Stretch <input type="checkbox"/>	

Please report any change of compression therapy and state reason why below AND complete a 'Change of Circumstances' form.

Has there been an **adverse event** since your last visit? Yes No

If **yes**, please complete the relevant form described at the beginning of this booklet

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Patient Trial Number

<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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VenUS III: Ultrasound Trial

DRESSING LOG BOOKLET (April 2006)

To be used for all patients allocated to Standard Care and patients allocated to Ultrasound AFTER their 12 weeks of Ultrasound

Booklet Number

<input type="text"/>	<input type="text"/>
----------------------	----------------------

- Please complete a page in the Dressing Log Booklet at each visit to the patient and complete the following trial documentation at the appropriate times.
- When the Reference ulcer has healed please complete an **Ulcer Healed Form**.
- When the last ulcer has healed (i.e. the patient is ulcer free) please complete an **Ulcer Healed Form**.
- If the only ulcer on the leg has healed please also complete a **Change of Circumstances Form**.
- If there are unhealed ulcers on the leg, continue to complete the Dressing Log Booklet until all ulcers have healed - when this occurs please complete a **Change of Circumstances Form**.
- If the reference ulcer is not healed in 12 months please complete a **Change of Circumstances Form**.

Please report any patient event observed today and complete the relevant form. Please ensure you adhere to your employing Trust's adverse event procedure.

A list of possible adverse events is listed below. This is NOT an exhaustive list. If you suspect an event is serious please contact the trial manager. We would rather you err on the side of caution and report an adverse event.

Please complete a Non-Serious Adverse Event (NSAE) form for any of the following:

Pressure damage

Infection

Skin damage surrounding ulcer

New ulcer

Ulcer deterioration (Please also complete a 'Change of Circumstances Form')

Patient had experienced an adverse reaction to the ultrasound treatment or contact gel (Please also complete a 'Change of Circumstances Form')

Please complete a Serious Adverse Event (SAE) form for any of the following:

Patient has died (Please also complete a 'Change of Circumstances Form')

Patient has been admitted to hospital for more than 24 hours (Please also complete a 'Change of Circumstances Form')

Limb compromise

Life - threatening event

Persistent or significant disability/incapacity

Patient is a newly diagnosed diabetic

Please note this is not an exhaustive list, if you suspect an event is serious, please contact the Trial Manager at the York Trials Unit. We would rather you err on the side of caution and reported an event to us.

If the patient has had any change in treatment (deviating from the protocol) please complete a 'Change of Circumstances Form'

Data collection checklist

For each visit, please complete a new page in this booklet recording the treatment applied.

Every 4 weeks from the first trial treatment (first day of treatment equals Day 0), please take a **digital photograph** of the **REFERENCE ULCER**.

Every 4 weeks from the first trial treatment (i.e. at the same time as taking the photograph of the reference ulcer), please take **tracings** of **ALL** the leg ulcers the patient has.

These key data collection times can also be seen in the "**Record of data collected for a recruited patient**" form which should be kept in the front of the patient's records.

DRESSING LOG
PLEASE COMPLETE THIS FORM EVERY TIME A PATIENT IS SEEN BY A NURSE
FOR LEG ULCER TREATMENT

Date of Visit

		/			/		
<i>day</i>			<i>month</i>			<i>year</i>	

Location (place a cross in one box only)

Home	<input type="checkbox"/>	GP Surgery	<input type="checkbox"/>
Leg ulcer clinic	<input type="checkbox"/>	Leg ulcer club	<input type="checkbox"/>
Nursing Home	<input type="checkbox"/>	Other (specify below)	<input type="checkbox"/>

Knitted viscose dressing (KVD) applied Yes No

Please report any change to the primary dressings and state reasons why below (please put name of primary dressing/wound contact layer/topical agent applied apart from a KVD) AND complete a 'Change of Circumstances' Form

Compression bandages applied (please cross one box only):

4 layer high compression	<input type="checkbox"/>	3 layer reduced compression	<input type="checkbox"/>
3 layer high compression	<input type="checkbox"/>	Low compression	<input type="checkbox"/>
2 layer high compression	<input type="checkbox"/>	No compression	<input type="checkbox"/>
Short Stretch	<input type="checkbox"/>		

Please report any change of compression therapy and state reason why below AND complete a 'Change of Circumstances' form.

Has there been an **adverse event** since your last visit? Yes No

If **yes**, please complete the relevant form described at the beginning of this booklet

<p>Date</p> <table style="margin: auto;"> <tr> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="text-align: center;">/</td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="text-align: center;">/</td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> </tr> <tr> <td colspan="2" style="text-align: center;"><i>day</i></td> <td></td> <td colspan="2" style="text-align: center;"><i>month</i></td> <td></td> <td colspan="4" style="text-align: center;"><i>year</i></td> </tr> </table>			/			/					<i>day</i>			<i>month</i>			<i>year</i>				<p>Patient Trial Number</p> <table style="margin: auto;"> <tr> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="text-align: center;">-</td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> <td style="border: 1px solid black; width: 20px; height: 20px;"></td> </tr> </table>			-				
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<i>day</i>			<i>month</i>			<i>year</i>																						
		-																										

VenUS III: Ultrasound Trial - Change of Circumstances Form - Version 2 (March 2006)

Please complete this form if there are any changes in the circumstances of the VenUS III participant.

Reason for change in circumstance:

Please read the following and write the number of the **MAIN** reason in the box at the end of this form.

1. The patient no longer wishes to: *(please tick all that apply)*
 - a) **Have the trial treatment**
NB: this is not the same as change of treatment due to clinical needs - see options 5, 6 or 7
 - b) **Complete their postal questionnaires**
 - c) **Have data collected by the nurse about their ulcer(s)**
e.g. ulcer tracings/ photos/dressing log booklets
2. **Patient has experienced an Adverse Event** *(Please also complete either a 'Non-serious Adverse Events Form' or a 'Serious Adverse Events Form' - refer to inside cover of dressing log booklet for guidelines as to which is appropriate. If still unsure, please telephone York Trials Unit)*
3. **The patient is ulcer free** *(Please also complete an 'Ulcer Healed Form')*
4. **Patient has been in the trial for 12 months and is therefore being withdrawn** *(May still have ulcers on their legs)*
5. **Patient's ulcer has increased in area for two consecutive weeks and therefore treatment has been changed** *(Please provide details in treatment/ dressing log)*
6. **Patient's ulcer has deteriorated and therefore treatment has been changed** *(Please provide details in treatment/ dressing log)*
7. **Treatment has changed due to a reason other than options 5 or 6** *(Please provide details in treatment/ dressing log)*
8. **Patient is lost to follow-up**
9. **Patient has died** *(Please also complete a 'Serious Adverse Events Form')*
10. **Other reason** *(please state)*

The MAIN reason for the change is option number	<input style="width: 20px; height: 20px;" type="text"/>	(Please write option number in box)
Please give more details, if applicable: 		
Is the patient completely ulcer free?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
If NO , please take a tracing of all unhealed ulcers and a digital photo of the reference ulcer if it is unhealed		
Please confirm that you have traced all unhealed ulcers (and photographed reference ulcer if unhealed) and attached the tracings to the back of this form	<input type="checkbox"/> Yes	<input type="checkbox"/> No

Please send this form and all patient documentation to your local research nurse

Date form completed

		/			/		
<i>day</i>			<i>month</i>			<i>year</i>	



**VenUS III: Ultrasound Trial -
Ulcer Healed Form**

Patient Trial Number

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 -

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PLEASE complete this form when:

- a) The Reference Ulcer has healed and / or**
- b) The last ulcer has healed (i.e. the patient is ulcer free)**

1) Has the Reference ulcer healed today ? Yes No
(i.e. the largest ulcer at the baseline visit)

If yes, please take a DIGITAL PHOTOGRAPH of the reference ulcer and confirm that you have done so below.

Please confirm you have taken a digital photograph of the healed reference ulcer

Yes No

Please make sure that you have included on the colour target card, the:

- date,
- patient trial number,
- ulcer ID (e.g. R1, R2 etc).

Send the compact flash card to your local research nurse for storage.

2) Has the last ulcer healed today? Yes No
(i.e. the patient is ulcer free)

If no, please continue to complete the dressing log until the patient is free from ulcers on both legs. When the patient is ulcer free on both legs, please complete another **Ulcer Healed Form**

If yes, please complete the **Change in Circumstances Form** to inform us of trial completion

NOTE: You do not need to inform us of the dates of healing of any non-reference ulcers until the patient has healed **all** their leg ulcers (i.e. - they are ulcer free)

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THE UNIVERSITY *of York*

CONFIDENTIAL

VenUS III Ultrasound Study

Three Month Questionnaire

Participant ID Number

<input type="text"/>	<input type="text"/>	-	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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This unique number will be allocated to the patient when the nurse telephones the randomisation service.

Nurse: Please enter the number in the boxes above after you have been given it by the randomisation service.

Date

<input type="text"/>	<input type="text"/>	/	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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VenUS III (Venous Ulcer Studies III - Ultrasound for venous leg ulcers)
A multicentre randomised trial, funded by the NHS Health Technology Assessment Programme
(International Standardised Randomised Controlled Trial No: 21175670 & EudraCT No. 2004-004911-51)

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PLEASE READ ALL THE INSTRUCTIONS BEFORE COMPLETING THE QUESTIONNAIRE

Thank you for agreeing to take part in this study.

We would like to find out a little about your health and how your leg ulcer might affect your life.

Please answer **ALL** the questions. Although some of the questions may not seem relevant to yourself, they do give us valuable information about your leg ulcer.

If you find it difficult to answer a question, please do the best you can.

Please follow the instructions for each section carefully.

For each section, if you are asked to put a cross in the box, please use a cross rather than a tick, as if you were filling out a ballot paper.

For example, in the following question, if your answer to the question is yes, you should place a cross firmly in the box next to yes.

Do you drive a car? **Yes**
 No

If you are asked to circle a number, please use a circle rather than underlining a number.

For example, in the following question, if you are asked 'How happy are you today?' where '1' is 'very unhappy' and '5' is 'very happy'. If you feel neither happy nor unhappy you may wish to answer '3'. You do this by clearly circling the number 3.

1 2 3 4 5

PLEASE USE A BLACK OR BLUE PEN FOR ALL OF THE QUESTIONS.

Please do not use a pencil or any other coloured pen.

Please read all the instructions for each section.

This section asks about your health in general. By placing a cross in one box in each group below, please indicate which statement best describes your own health state today.

Do not cross more than one box in each group.

Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

These questions ask for your views about your health. This section will help us keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking a cross in the appropriate box. If you are unsure on how to answer a question, please give the best answer you can.

1. In general, would you say your health is:
(please cross one box only)

Excellent	Very Good	Good	Fair	Poor
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. During a typical day does **your health** limit you in **moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf? If so, how much?
(please cross one box only)

Yes, limited a lot	Yes, limited a little	No, not limited at all
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. During a typical day does **your health** limit you in climbing **several** flights of stairs? If so, how much?
(please cross one box only)

Yes, limited a lot	Yes, limited a little	No, not limited at all
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. During the **past 4 weeks**, how much of the time have you accomplished less than you would like in regular daily activities **as a result of your physical health**?
(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. During the **past 4 weeks**, how much of the time have you been limited in performing any kind of work or other regular daily activities **as a result of your physical health**?
(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6. During the **past 4 weeks**, how much of the time have you accomplished less than you would have liked in your work or any other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?
(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

7. During the **past 4 weeks**, how much of the time have you done work or other activities less carefully than usual **as a result of any emotional problems** (such as feeling depressed or anxious) ?

(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (both outside the home and housework) ?

(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

9. This question is about how you feel and how things have been with you during the **past 4 weeks**. Please give the one answer that comes closest to the way you have been feeling. How much during the **past 4 weeks** have you felt calm and peaceful ?

(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

10. This question is about how you feel and how things have been with you during the **past 4 weeks**. Please give the one answer that comes closest to the way you have been feeling. How much during the **past 4 weeks** did you have a lot of energy ?

(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

11. This question is about how you feel and how things have been with you during the **past 4 weeks**. Please give the one answer that comes closest to the way you have been feeling. How much during the **past 4 weeks** have you felt downhearted and depressed ?

(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

12. During the **past 4 weeks** how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives etc.) ?

(please cross one box only)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please enter today's date

		/			/				
<i>day</i>			<i>month</i>			<i>year</i>			

In order to accurately measure the cost of different leg ulcer treatments, we would like to know the number of times you have seen a health professional (e.g. doctor or nurse) **not** as part of this study.

- In the **past 4 weeks** have you seen a doctor at your **doctor's surgery** OR seen a **doctor at home** for any reason relating to your health ?

Yes

No

If **Yes**, how many times...

have you seen a doctor at the surgery ?

have you been visited at home by a doctor ?

Were any of these visits because of your leg ulcer ?

Yes

No

If **Yes**, how many times ?

- In the **past 4 weeks** have you seen a nurse at your **doctor's surgery** OR seen a **nurse at home** for any reason relating to your health ?

Yes

No

If **Yes**, how many times...

have you seen a nurse at the surgery ?

have you been visited at home by a nurse ?

Were any of these visits because of your leg ulcer ?

Yes

No

If **Yes**, how many times ?

3. In the **past 4 weeks** have you **been to hospital as an outpatient** for any reason relating to your health ?

Yes

No

If **Yes**, how many times...

Were any of these visits because of your leg ulcer ?

Yes

No

If **Yes**, how many times...

4. In the **past 4 weeks** which of the following have helped you around the house, to do the shopping etc. ?
(place a cross in the box for all of those who have helped and then enter the number of hours per week they have helped you. If you have not needed any help put a cross in the 'I have not needed any help' box)

I have not needed any help

Home help approximately how many hours per week

Relative approximately how many hours per week

Friend/ neighbour approximately how many hours per week

Other approximately how many hours per week

If you have selected 'Other' please state relationship in box below)



THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

If you have any general comments about your ulcer, the study, or this questionnaire, please write them below.



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8



VenUS III: Ultrasound Trial



NON-SERIOUS ADVERSE EVENT FORM

Patient concerned (Trial number) -

Name of nurse reporting event

Name of Local Research Nurse (if different from above)

Date of event / /
day month year

Details of event

Action taken

Do you think the event is related to the trial treatment (contact gel or ultrasound therapy)?
 (please tick only ONE box)

Unrelated	Unlikely to be related	Possibly related	Probably related	Definitely related	Not able to assess if related
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If the AE has resulted in any of the following you must complete a Serious Adverse Event (SAE) form instead:

- death
- a life-threatening risk (that is an immediate risk of death)
- hospitalisation of patient
- persistent or significant disability / incapacity
- other medically important condition

Possible SAEs in the VenUS III trial. Please note this is not an exhaustive list. If you suspect an event is serious, please contact the Trial Manager at the York Trials Unit. We would rather you erred on the side of caution and reported an event to us.

VenUS III: Ultrasound Trial

REVIEW OF NON-SERIOUS ADVERSE EVENT

Patient concerned
(Trial ID number) -

How and when notification
of the event was made

Date of review / /

Day Month Year

Action taken

Signature of reviewer

For York use only

Date reviewed by Trial
Management Group / /

Day Month Year

VenUS III: Ultrasound trial



SERIOUS ADVERSE EVENT FORM

Patient Trial Number -

Date of birth Male Female

day month year

Date of onset of event

day month year

Description of event:

Classification of SAE: (tick all that apply)

Death Life or limb threatening event Hospitalisation required /prolonged

Persistent or significant disability/incapacity Other medically important condition

PLEASE OBTAIN COPIES OF ANY AVAILABLE SUPPORTING DOCUMENTS RELATING TO THE EVENT FOR FORWARDING TO THE VENUS III TRIAL MANAGER.

Please state outcome of event at time of this report (tick one box only) **Date recovered / died**

Recovered fully	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Recovered partially	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Died	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Ongoing	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
		<small>day</small>	<small>month</small>	<small>year</small>	

Relationship of event to treatment (tick one box only)

Unrelated Unlikely to be related Possibly related Probably related Definitely related Not able to assess if related

York Trials Unit must be notified of any serious adverse event by telephone (01904 321 306) within 24 hours of onset of the event.

Post or fax the top copy of this form and any available supporting documents to Dr Jude Watson, Trial Manager, Department of Health Sciences (Area 4), Seebohm Rowntree Building, University of York, Heslington, YORK YO10 5DD, within 48 hours of onset (Fax no: 01904 321387).

Please note that we may need to inform your Local Research Ethics Committee of this event.

Final date of resolution if known:

day month year

Outcome if known: Recovered fully Recovered partially

Possible SAEs in the VenUS III trial:

Patient has died; Limb compromise (limb requires revascularisation or amputation); **Newly diagnosed diabetic** (patient diagnosed as diabetic by GP during course of trial); **Patient hospitalised for longer than 24 hours for any reason.**

**Please note this is not an exhaustive list, if you suspect an event is serious or are unsure, please contact the Trial Manager at the York Trials Unit. We would rather you erred on the side of caution and reported an event to us. **

Local Researcher's name (block capitals)

Local Researcher's signature

1 copy to be sent to the Trial manager at the York Trials Unit, 1 copy to be kept in patient's notes and 1 copy to be kept by Local Research Nurse.

VenUS III: Ultrasound Trial

REVIEW OF SERIOUS ADVERSE EVENT

Patient concerned
(Trial ID number) -

How and when notification
of the event was made

Date of review / /

day month year

Action taken

Signature of reviewer

For York Use Only





Date reviewed by TSC
And DMEC / /

Appendix 6

Ultrasound protocol

VenUS III: Ultrasound Trial
Quick guide to applying the ultrasound treatment

Version 2

1. Set up the ultrasound machine by plugging mains lead into the back (unless you want to use the built in battery) and the lead of the transducer head into the output socket on the front of the machine -  Place transducer head into the holder on unit.
2. Position patient's limb on a pillow/ foot rest.
3. Visually inspect the wound and check for contraindications
4. If this is the patient's **first** treatment session, take a digital photo of the **reference** ulcer, tracings of **all** the ulcers and calculate the duration of ultrasound treatment for the reference ulcer according to its size. This should be repeated **every 4 weeks**.
5. Clean the face of the transducer with 70% isopropyl alcohol (e.g. sterile swab)
6. Apply contact gel to the face of the transducer and the skin **around** the ulcer.
7. Smooth the gel over the **skin surrounding the ulcer** using the transducer face.
8. Switch on the ultrasound machine with a long press of the power button - 
9. Explain to the patient that they should not feel anything when the treatment starts. If they feel pain or heat, they must tell you straight away.
10. Place the transducer head on the skin.
11. Set the **timer** (clock symbol that is highlighted when machine is first switched on) according to the size of the ulcer, by turning the rotary control clockwise.
12. Press the up button () to move up to the **output** display –  and set to **0.5 W/cm²** by turning the rotary control clockwise
13. Move the transducer *in a slow and controlled manner* **around the edges of the wound** in overlapping circles to cover the skin evenly.
14. Always ensure the transducer face is in contact with the skin and that there is adequate contact gel present.
15. When timer has finished its countdown, lift the transducer off the leg.
16. Switch off the machine with a short press of the power button.
17. Wipe the excess gel from the transducer face with a tissue or swab. Clean it with 70% isopropyl alcohol and place into holder on unit. Wipe excess gel from the patient's leg.
18. Inspect skin for undue reddening.
19. Record the ultrasound treatment time and the dose in the patient records.
20. Apply dressing and bandage as usual.

VenUS III: Ultrasound Trial Quick guide to the care of the ultrasound machine
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1. Check daily that the machine is working by covering the transducer head with a fine layer of contact gel. Turn the machine on, set the timer to any length, select the output display by using up button (▲) and turn the intensity up until you see the gel move. This means the machine is working. Turn off and clean the transducer head.
2. Always ensure that you clean the face of transducer head with 70% isopropyl alcohol before and after use.
3. When you have finished treatment, you may find it useful to place the handle end of the transducer into the large round hole on the machine, as this will prevent transfer of gel onto any surfaces prior to its cleaning. When the head is clean, it can be placed face first into the same hole and clicked into place.
4. Please ensure that the ultrasound machine, mains cable, transducer head and contact gel are all returned to the carry case after treatment.
5. When not being charged and when not in use, please keep the ultrasound machine in its carry case.
6. On return to base, the battery should be recharged. The manufacturers recommend charging the battery when it is cold e.g. first thing in the morning. However this is not essential and the machine should be recharged at your convenience.

Calculating the length of ultrasound treatment for the reference ulcer

Area of ulcer	Treatment time
5cm ² or less	5 minutes
6cm ²	6 minutes
7cm ²	7 minutes
8cm ²	8 minutes
9cm ²	9 minutes
10cm ² and over	10 minutes

The treatment time should be calculated at the **first** treatment session and then recalculated **every 4 weeks** thereafter – i.e. on the visits when a digital photo and tracings are scheduled to be taken.

Appendix 7

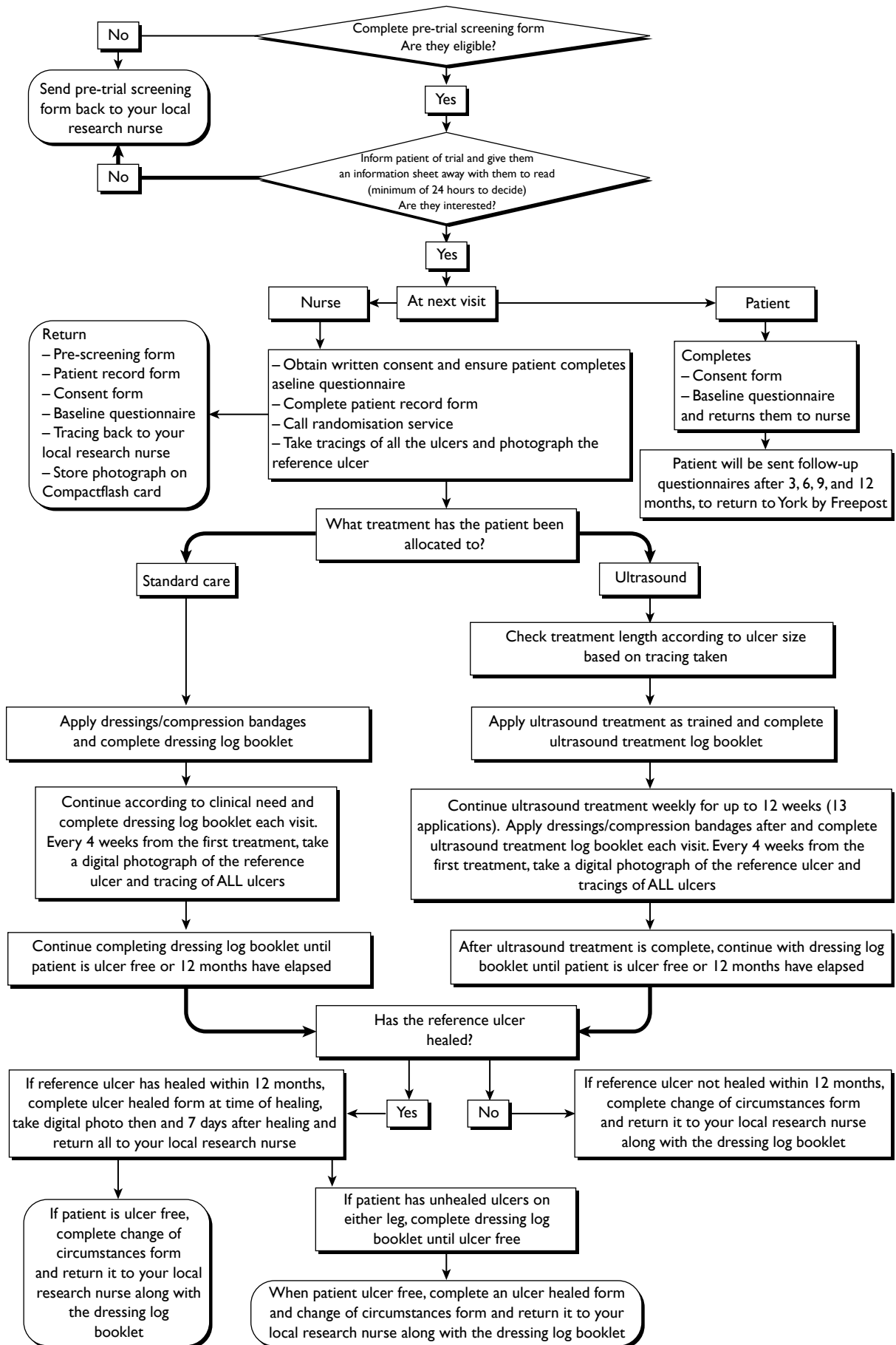
Site training

Site	Date of training session (number trained)	Date of training session (number trained)	Date of training session (number trained)
Bolton	23 November 2005 (10)		
Scarborough	9 January 2006 (9)		
Cumbria	7 February 2006 (2)		
WHST	20 February 2006 (2)		
Leeds	17 March 2006 (24)	22 September 2006 (1)	
Hull	11 May 2006 (3)	19 May 2006 (2)	23 October 2007 (1)
Dunfermline	9 June 2006 (3)		
Nottingham	31 July 2006 (3)		
South Essex	11 September 2006 (7)		
Birmingham	20 October 2006 (3)	3 July 2007 (1)	11 February 2008 (1)
Bradford	6 November 2006 (2)		
Dublin	9 January 2007 (4)		

WHST, Western Health and Social Care Trust.

Appendix 8

Flow chart for VenUS III trial



Below is a summary of what completed paperwork should be returned to which person, for each given scenario of patient involvement.

Patient not eligible or not interested at the first mention of trial	Return to your local research nurse: ➤ A completed and signed Pre-screening Form
Patient eligible in principle, but unsure, then not interested after 48 hours	Return to your local research nurse: ➤ A completed and signed Pre-screening Form
Patient eligible in principle, interested enough to attend full explanation but then not interested	Return to your local research nurse: ➤ A completed and signed Pre-screening Form
Patient fully eligible and consenting	Return to your local research nurse: ➤ A completed and signed Pre-screening Form ➤ A completed and signed Patient Record Form ➤ A signed and witnessed Patient Consent Form ➤ A completed Patient Baseline Questionnaire ➤ A completed Tracing of ulcer
Patient's reference ulcer has healed and there are no other ulcers The patient is now completely ulcer free	Return to your local research nurse: ➤ A completed Ulcer Healed Form ➤ Card with digital photos of reference ulcer site taken at time of healing and also 7 days after healing ➤ A completed Change of Circumstances Form ➤ A completed Dressing or US Treatment Log Booklet
Patient's reference ulcer has healed, but they still have other ulcers	Return to your local research nurse: ➤ A completed Ulcer Healed Form ➤ Card with digital photos of reference ulcer site taken at time of healing and also 7 days after healing
Change in patient's circumstances Including: treatment withdrawals, ulcer deterioration, adverse reactions, hospitalisation, patient death and lost to follow-up.	Return to your local research nurse: ➤ A completed Change of Circumstances Form
Patient has had an adverse event	Return to your local research nurse: ➤ A completed Change of Circumstances Form ALSO ➤ If non-serious - Inform your local research nurse. With the assistance of your local research nurse, complete a Non-serious Adverse Event Form . The local research nurse should return this form to the York Trials Unit within 5 days. ➤ If serious - Inform your local research nurse immediately . Your local research nurse should inform the York Trials Unit by telephone within 24 hours. With the assistance of the local research nurse, the Local Investigator should complete and sign a Serious Adverse Events Form . This form should be faxed to the York Trials Unit within 48 hours.

Other forms you have been provided with are:

Record of data collected for a recruited patient	To act as a reminder and for you to record which data should be recorded at each visit to a patient participating in VenUS III. This form should be kept at the front of the patient's records and does not need to be returned to anyone.
---	--

Version 7 Jan 2006

Appendix 9

Digital image and tracing protocol

VenUS III ultrasound trial

Protocol for digital photographs and tracings of ulcers

At baseline (week 1 – first day of treatment equals day 0):

- please take a **digital photograph** of the **reference ulcer** (largest) AND
- **tracings** of **all** the ulcers the patient has.

Every **4 weeks** from the first trial treatment:

- please take a digital photograph of the reference ulcer AND
- **tracings** of **all** the ulcers the patient has.

i.e. each time you take a photograph of the reference ulcer you should also take tracings of all the ulcers.

If the reference ulcer heals:

- please take a digital photograph to confirm this on the **day of healing** AND
- take another digital photograph **7 days later**.

If there are still other unhealed ulcers on the patient's leg:

- please continue to take **tracings** of the ulcers every 4 weeks as usual and complete dressing log booklets at each visit until they become ulcer free OR one year has passed since they first started in the trial.

NOTE

Please remember to always include a colour target card in the photograph, with the date, patient's trial number and ulcer ID (e.g. R1 or R2) written on it.

AND

Please write the same information on the acetate grid when you take the tracings.

Appendix 10

Ultrasound machine acceptance testing and 3-monthly servicing

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MEASUREMENTS

Output Power

The power radiated by each EMS therapy unit was measured against the NPL Reference Balance. Each was configured according to the output settings specified in the RESULTS section of this certificate. This report is only valid for these output settings.

The transducer was mounted in the top of the balance so that it radiated vertically downwards. The acoustic power radiated in the forward direction was measured using the NPL Reference Balance, with the tank filled with degassed, deionised water. The balance was fitted with an absorbing target manufactured from NPL absorber. The separation between the transducer face and the target was between 5 and 10 mm approximately. The experimental arrangement (with an NPL reference transducer under test) is shown in Figure 1.

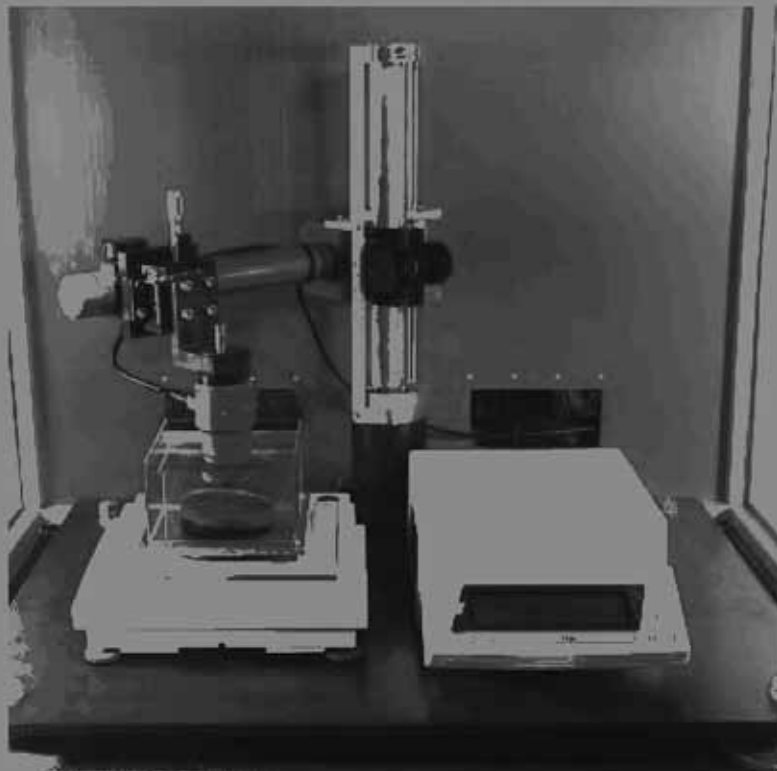


Figure 1: NPL Reference Balance

Reference: U2263

Checked by: *MM* *SC*

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The EMS unit and transducer were switched on for at least 1 hour (with the output of the unit switched off) prior to measurement in order for the drive unit and treatment head to reach thermal equilibrium. Measurements were made by recording the mean change in the NPL Balance reading produced by switching the EMS unit ON and OFF. The balance was interfaced to a PC and the change in weight of the target recorded as a function of time for the duration of each measurement set. The resulting data set was analysed using an extrapolation technique to determine the change in the radiation force at each ON-OFF and OFF-ON transition. An equivalent acoustic power for each transition was calculated and the mean value was taken to be the measured power from the transducer. A measurement set consisted of at least four ON-OFF transitions. Two independent sets of measurements were made at each excitation setting with the transducer being removed from the NPL Balance between each measurement set. There was no significant difference observed between the ON-OFF and OFF-ON readings.

Measurements were made with the physiotherapy system operating at a nominal output setting of 0.5 W cm^{-2} , in continuous wave (CW) mode, and in 1:4 pulsed wave (PW) mode.

Note: The transducer was energised at the start of each ON period by rotating the output control so that the appropriate nominal power level as stated in the RESULTS section was indicated on the display. At the end of the ON period the output control was rotated back to zero.

Reference: U2263

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Effective radiating area determination

To determine the effective radiating area (A_{ER}), the acoustic power radiated in the forward direction was measured using the NPL Therapy-Level Balance, with the tank filled with degassed, deionised water. The balance was fitted with a reflecting target of 60 mm diameter. The balance was used in conjunction with the NPL Apertures (see Figure 2), which selectively attenuate concentric regions of the radiated field, thereby allowing the determination of the output power as a function of aperture diameter. The separation between the transducer face and the aperture, and between the output surface of the aperture and the target, was approximately 2 mm in each case. The EMS unit was switched on for at least 1 hour (with the output of the unit switched off) prior to measurement in order for the drive unit and treatment head to reach thermal equilibrium.



Figure 2: NPL Apertures for effective radiating area determination

For each aperture size chosen, the transducer was mounted in the top of the balance, above the aperture, so that it radiated vertically downwards. A schematic diagram of the experimental set up is shown in Figure 3.

Reference: U2263

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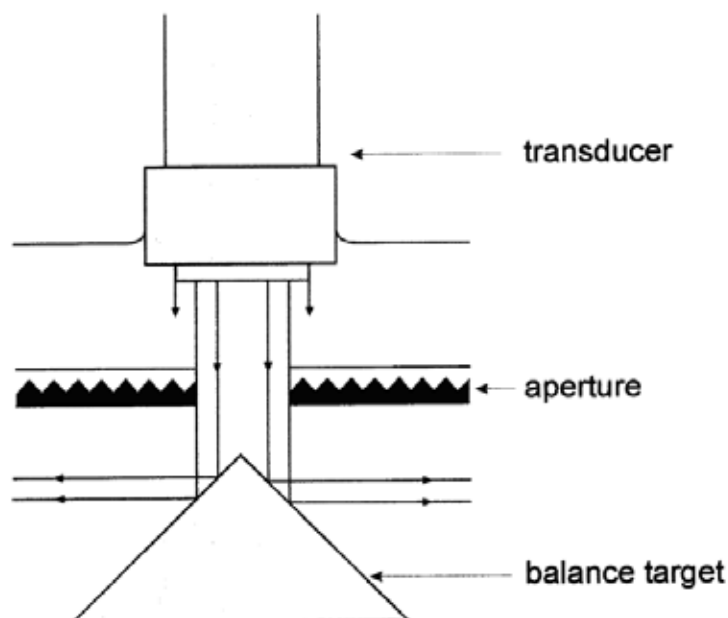


Figure 3: Schematic diagram of aperture arrangement

Measurements of output power for each aperture size were then made by recording the mean change in the balance reading (in units of watts) produced by switching the unit ON and OFF. A measurement set consisted of two OFF-ON-OFF transitions. There was no significant difference observed between the ON-OFF and OFF-ON readings. Measurements were made using the physiotherapy system under test in CW mode only. For each physiotherapy system, a minimum of 12 aperture diameters was used to determine a value for A_{ER} , using an analysis technique analogous to that described in standard IEC 61689.

Reference: U2263

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RESULTS

System details	Output settings	Nominal Power	Output Power	Effective radiating area
90566/91471	CW, 0.5 W cm ⁻²	2.0 W	2.2 W ± 5 %	4.1 cm ² ± 10 %
	PW 1:4, 0.5 W cm ⁻²	0.4 W	0.46 W ± 5 %	
90255/88874	CW, 0.5 W cm ⁻²	2.0 W	2.2 W ± 5 %	4.2 cm ² ± 10 %
	PW 1:4, 0.5 W cm ⁻²	0.4 W	0.44 W ± 5 %	

The mean temperature of the water within the balance tank during measurements was 22.0 ± 0.5 °C.

The reported uncertainty in output power is based on a standard uncertainty multiplied by a coverage factor, $k=2$, providing a level of confidence of approximately 95%. The reported uncertainty in the effective radiating area is an estimate of the overall uncertainty, based on reference measurements made using a similar experimental arrangement.

Reference: U2263

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EMIS Unit/ transducer	CW output power (W)	Deviation from nominal (%)	PW output power (W)	Deviation from nominal (%)	Effective radiating area (cm ²)	Deviation from nominal (%)	CW Effective Intensity (W/cm ²)	Deviation from nominal (%)	PW Effective Intensity (W/cm ²)	Deviation from nominal (%)
91902/91582	1.89	5.5	0.39	3.5	4.61	15.3	0.41	18.0	0.084	16.3
91905/91580	1.88	6.1	0.38	3.9	4.73	18.3	0.40	20.7	0.081	18.8
91898/91578	1.88	5.8	0.39	3.1	4.55	13.7	0.41	17.2	0.085	14.7
91906/91886	1.83	8.5	0.38	5.7	4.37	9.3	0.42	16.3	0.086	13.8
91907/91884	1.94	3.0	0.40	1.2	4.95	23.8	0.39	21.6	0.080	20.2
91863/91833	2.10	5.2	0.44	9.5	4.45	11.3	0.47	5.5	0.098	1.6
91864/91839	2.07	3.3	0.43	7.1	4.75	18.7	0.44	13.0	0.090	9.8
91904/91579	1.98	0.9	0.41	2.7	4.60	15.0	0.43	13.8	0.089	10.7
91873/91805	2.06	2.9	0.43	7.7	4.49	12.3	0.46	8.4	0.096	4.1
91814/91474	2.20	10.2	0.46	14.8	4.40	10.0	0.50	0.2	0.104	4.4
91867/91842	2.29	14.3	0.47	16.6	4.81	20.3	0.48	4.9	0.097	3.0
91903/91577	1.81	9.7	0.37	7.7	4.59	14.8	0.39	21.3	0.080	19.6
91899/91574	1.82	9.2	0.37	6.6	4.99	24.7	0.36	27.2	0.075	25.1
91872/91583	2.04	1.8	0.42	4.0	4.63	15.7	0.44	12.0	0.090	10.1
91868/91840	2.22	11.2	0.46	13.9	4.41	10.3	0.50	0.8	0.103	3.2
91870/91836	2.11	5.7	0.44	8.8	4.40	10.0	0.48	3.9	0.099	1.1
91866/91835	2.32	15.9	0.48	21.1	4.21	5.2	0.55	10.1	0.115	15.1
91865/91838	2.15	7.3	0.45	11.2	4.44	11.0	0.48	3.3	0.100	0.2
91869/91841	2.05	2.6	0.42	5.2	4.41	10.3	0.47	7.0	0.095	4.6

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Reference: U2310

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EMIS Unit/transducer	CW output power (W)	Deviation from nominal (%)	PW output power (W)	Deviation from nominal (%)	Effective radiating area (cm ²)	Deviation from nominal (%)	CW Effective Intensity (W/cm ²)	Deviation from nominal (%)	PW Effective Intensity (W/cm ²)	Deviation from nominal (%)
91876/91806	2.11	5.5	0.44	8.9	4.27	6.7	0.49	1.1	0.102	2.1
91817/91810	2.28	14.0	0.47	16.4	4.90	22.4	0.47	6.9	0.095	4.9
91816/91993	2.06	2.8	0.42	4.9	4.49	12.2	0.46	8.4	0.094	6.5
91871/91575	1.94	3.0	0.40	0.4	4.43	10.7	0.44	12.4	0.090	10.0
91815/91991	2.22	10.9	0.46	15.1	4.37	9.2	0.51	1.6	0.105	5.4
91900/91581	1.88	6.2	0.38	4.9	4.36	9.0	0.43	13.9	0.087	12.8
91874/91809	2.11	5.5	0.44	9.6	4.56	14.0	0.46	7.4	0.096	3.8
91901/91576	1.86	7.2	0.38	4.8	4.69	17.3	0.40	20.9	0.081	18.9
91875/91803	2.17	8.7	0.45	11.3	4.21	5.3	0.52	3.2	0.106	5.7
91818/91807	2.20	9.8	0.46	13.7	4.17	4.3	0.53	5.2	0.109	9.0
91878/91804	2.24	11.9	0.46	14.0	4.41	10.2	0.51	1.5	0.103	3.4
91820/91808	2.20	9.9	0.46	14.4	4.76	19.0	0.46	7.6	0.096	3.8
91881/91883	2.04	2.1	0.42	5.8	4.19	4.7	0.49	2.4	0.101	1.1
91879/91801	2.21	10.6	0.45	13.3	4.24	6.0	0.52	4.3	0.107	6.9
91812/91990	1.97	1.5	0.40	0.3	4.89	22.3	0.40	19.4	0.082	18.0
91813/91994	2.02	1.0	0.42	4.9	4.98	24.4	0.41	18.8	0.084	15.7
91882/91887	2.20	9.9	0.45	12.2	4.22	5.6	0.52	4.1	0.106	6.3
91877/91802	2.08	3.8	0.43	6.5	4.27	6.7	0.49	2.7	0.100	0.2
91811/91995	2.24	12.2	0.46	15.7	5.13	28.2	0.44	12.5	0.090	9.7

Reference: U2310

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Continuation Sheet

EMS Unit/ transducer	CW output power (W)	Deviation from nominal (%)	PW output power (W)	Deviation from nominal (%)	Effective radiating area (cm ²)	Deviation from nominal (%)	CW Effective intensity (W/cm ²)	Deviation from nominal (%)	PW Effective intensity (W/cm ²)	Deviation from nominal (%)
91811/92216	2.32	16.0	0.48	20.0	4.72	18.0	0.49	2.0	0.102	2.0
91813/92210	2.21	10.5	0.46	15.0	4.63	15.8	0.48	4.0	0.099	1.0
91867/92002	2.17	8.5	0.45	12.5	4.29	7.3	0.51	2.0	0.105	5.0
91901/91576	2.01	0.5	0.42	5.0	4.29	7.3	0.47	6.0	0.098	2.0
91899/92217	2.18	9.0	0.45	12.5	4.33	8.3	0.50	0.0	0.104	4.0
91903/91577	2.09	4.5	0.42	5.0	4.37	9.3	0.48	4.0	0.096	4.0
91905/91580	2.06	3.0	0.42	5.0	4.63	15.7	0.45	10.0	0.091	9.0
91812/92220	2.19	9.5	0.45	12.5	4.20	5.0	0.52	4.0	0.107	7.0
91866/92212	2.16	8.0	0.44	10.0	4.80	20.0	0.45	10.0	0.092	8.0
91817/92196	2.28	14.0	0.48	20.0	5.04	26.0	0.45	10.0	0.095	5.0
91907/92218	2.21	10.5	0.46	15.0	4.17	4.3	0.53	6.0	0.110	10.0

Reference: U2419

Checked by: *446 JCS*

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Continuation Sheet

RESULTS

The nominal values for each parameter based on the specification supplied by the manufacturer are shown below. Two values for the effective intensity of each unit are also provided and these were calculated from the output power (in CW and PW modes) divided by the effective radiating area (ERA).

		Deviation from nominal value	Combined Expanded Uncertainty
Continuous Wave (CW) output power	2.7W	34 %	± 6 %
Pulsed Wave (PW) output power	0.5W	36 %	± 6 %
Effective Radiating Area (ERA)	4.1 cm ²	2.3 %	± 10 %
CW Effective Intensity	0.65 W/cm ²	30 %	± 12 %
PW Effective Intensity	0.13 W/cm ²	30 %	± 12 %

The mean temperature of the water within the balance tank during measurements was between 20.0 °C and 20.1 °C. The uncertainty of this temperature is ±0.5°C.

The reported uncertainty in output power is based on a standard uncertainty multiplied by a coverage factor, $k=2$, providing a level of confidence of approximately 95%. The reported uncertainty in the effective radiating area is an estimate of the overall uncertainty, based on reference measurements made using a similar experimental arrangement.

Reference: U2617

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Checked by: *YCS* . *MLL*

NATIONAL PHYSICAL LABORATORY

Continuation Sheet

UNCERTAINTIES

The uncertainty values quoted in the RESULTS section for the determination of the output power produced by the EMS unit are the expanded overall measurement uncertainties in using the NPL Reference Balance. These are calculated at a confidence level of approximately 95% according to the method recommended in publication M3003 (Edition 1) of the United Kingdom Accreditation Service entitled 'The Expression of Uncertainty and Confidence in Measurement'.

The expanded uncertainty is determined using both type A (random) and type B (systematic) uncertainty evaluations. Type A uncertainty evaluations were calculated from measurements of the EMS unit against the NPL Reference Balance; the transducer was removed from the NPL Reference Balance and repositioned between measurement sets. Type B uncertainty evaluations relate to the measurement of the applied power using the NPL Reference Balance and include components such as the influence of reflections from the tank wall lining and attenuation in the water path between the transducer and the target.

Important note:

This test report applies to the ultrasonic power radiated into a "free-field" environment. The output power may be sensitive to the acoustic load presented to the transducer. When using this unit, particularly in combination with any ultrasound power balance with a membrane, an uncertainty of at least $\pm 10\%$ should be assigned to the acoustic output power.

Reference: U2617

Checked by: *JS* *ML*

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Machine ID number	Acceptance testing result (pass/fail)	Re-testing result (pass/fail)	3-monthly servicing and result						
15	Fail	Pass	Not returned for servicing						18 February 2008
16	Pass	Pass	24 August 2006	14 November 2006	6 March 2007	6 June 2007	23 August 2007	N/A	22 August 2008
17	Pass	Pass	19 January 2007	12 September 2007	7 January 2008	11 April 2008	18 July 2008	15 October 2008	26 January 2009 29 May 2009
18	Pass	Pass	19 January 2007						
19	Fail	Pass	4 January 2007	16 March 2006	25 June 2007	24 September 2007	17 December 2007	17 March 2008	9 June 2008
20	Pass	Pass	4 January 2007	16 March 2006	25 June 2007	24 September 2007	17 December 2007	17 March 2008	9 June 2008
21	Pass	Pass	23 July 2008	Sent out for site use when main units being serviced					
22	Pass	Pass	Sent out for site use when main units being serviced						
23	Fail	Fail	Not given out for site use						
24	Pass	Pass	18 February 2008	21 December 2008	26 February 2009				
25	Pass	Pass	Not given out for site use – fault with transducer head						
26	Pass	Pass	18 February 2008	21 December 2008	26 February 2009				
27	Pass	Pass	22 January 2007	23 April 2007	6 November 2007	4 January 2008	14 April 2008	15 September 2008	
28	Pass	Pass	23 April 2007	6 November 2007	4 January 2008	28 January 2008	14 April 2008	15 September 2008	
29	Fail	Pass	Not returned for servicing – site withdrew						
30	Pass	Pass	Not returned for servicing – site withdrew						
31	Pass	Pass	3 December 2007	23 July 2008	14 January 2009				

Machine ID number	Acceptance testing result (pass/fail)	Re-testing result (pass/fail)	3-monthly servicing and result
32	Pass	Pass	7 August 2008 8 December 2008
33	Pass	Pass	6 November 2007 10 January 2008 14 April 2008 13 August 2008 14 January 2009
34	Pass	Pass	7 January 2008 11 April 2008 18 July 2008 15 December 2008 26 January 2009 29 May 2009
35	Pass	Pass	19 November 2008
36	Fail	Pass	Not given out for site use
37	Fail	Pass	Not given out for site use
38	Pass	Pass	Not given out for site use
39	Pass	Pass	Not given out for site use
40	Fail	Pass	Not given out for site use

N/A, not available.

Fault = shaded cell; pass = white cell.

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