NCCHTA

18 April 2007

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 HbA1C level of less than 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 some-one for the trial as the patients 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

5. We decided to amend the primary outcome measure in the light of advice from the Trial Steering Committee (20th January 2006) and the Trial Management Group (03rd 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. 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.

6. 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.

7. 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 endpoints 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.

8. 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 five pound 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 retuning the questionnaire.

9. 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

10. 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 greater than 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.

11. 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".

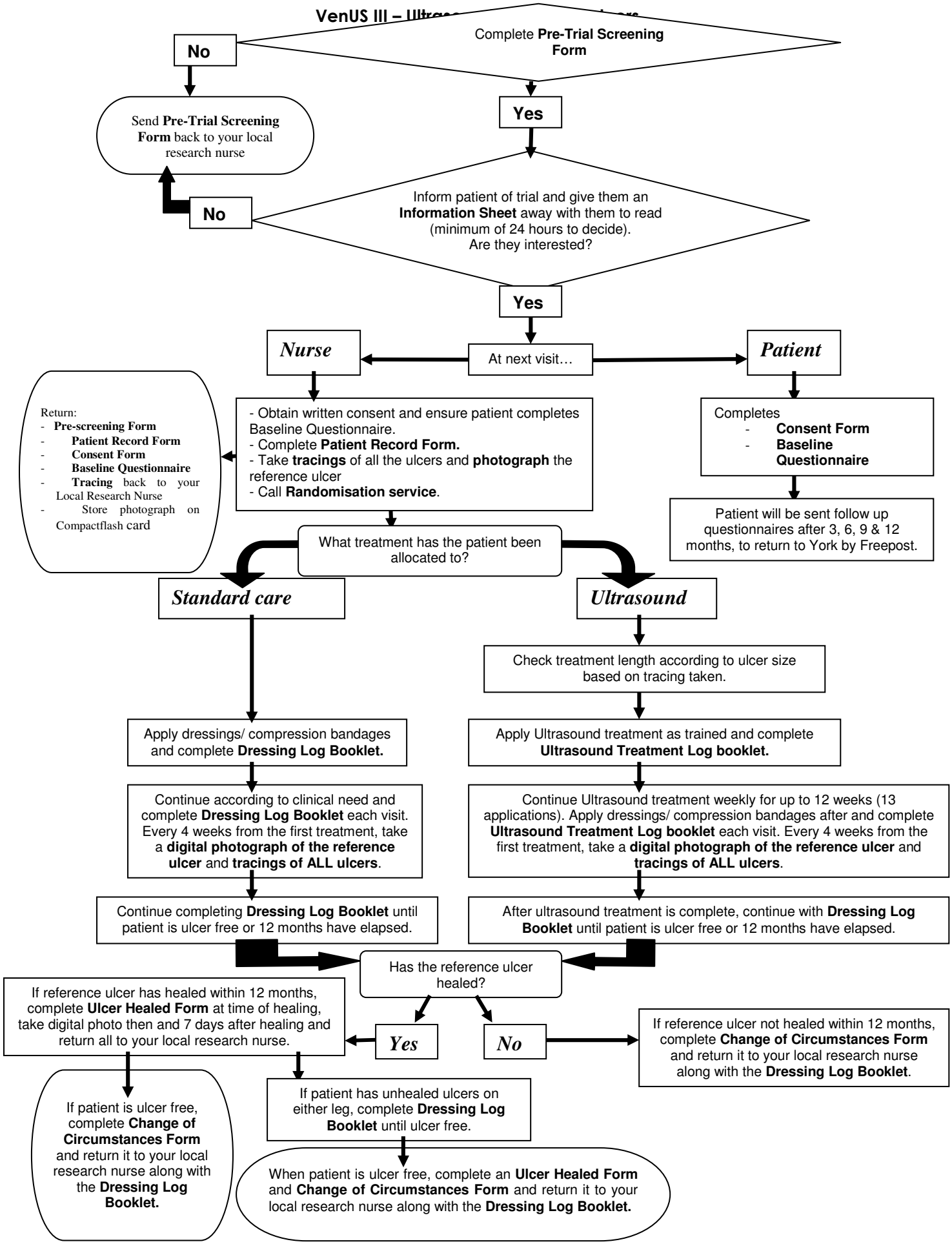

Figure 1 Flow diagram of trial recruitment & follow-up

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.[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 United Kingdom in 1989 was estimated to be between £150 million and £600 million 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% confidence interval (CI): 1.2-2.0).[5] Small (< 5cm^2 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 less than 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 (<5cm^2) 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 six 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 six 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 20Hz and 20,000Hz can be heard, however humans cannot detect frequencies below 20Hz; 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 700,000Hz and 4,000,000Hz (0.7 – 4.0 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 3MHz rather than 1MHz), reduces the penetration depth, by about 1/3rd (from 37mm to 12mm 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.[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 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 argues that there is no evidence from in vivo studies in humans that cavitation occurs at the ultrasound doses used for tissue repair.[11] 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 W/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 RCTs of ultrasound for treating venous leg ulcers. Seven of these were summarised in a systematic review by some of the applicants[18] 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 MHz: 0.3MHz was used in two trials (applied via water bath), 1MHz was used in four trials and 3MHz was used in another two trials. 1MHz has greater depth penetration than 3MHz. Ultrasound doses ranged between of 0.1 and 1.0 W/cm^2. In two trials in which a water bath ultrasound device was used, 0.1W/cm^2 was used. Doses of 0.5W/cm^2 were used in three trials and 1.0 W/cm^2 in four trials (one trial compared 0.5 and 1 W/cm^2 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 eight weeks and two for four 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 and cost effectiveness low dose ultrasound (0.5 W/cm^2 spatial average and temporal peak) delivered at 1MHz 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,
- 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, randomised controlled trial 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 six 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 Ankle-Brachial Pressure Index (ABPI) of greater than 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 > 5cm^2 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 greater than 6 months duration (determined by asking the patient), or

b) have a venous ulcer larger than 5cm^2 (estimated by tracing the ulcer outline onto a transparent grid with 1cm lines; nurse training will include standard tracing techniques / calculation of area).

Patients with ulcers that fulfil both criteria (> 5cm^2 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 greater than 6 months duration,

f) a venous ulcer larger than 5cm2

g) Doppler-determined ABPI of at least 0.8 within last three 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 quality of life tools will still be eligible to participate, but we will not collect quality of life data from them (the 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 (HbA1C) 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 $5cm^2$
4. Whether ulcer has been present for more or less than 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 4 and 6. 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 four weeks, at healing (or 12 months, whichever is sooner) and after 7 days post healing (if healed). Research nurses will collect recurrence data at six and 12 months.

Quality of life data (HRQoL) will be collected via postal survey at three, six, nine 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.

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 quality of life, end of ultrasound treatment
3	6 months	Assessment of recurrence and quality of life
4	9 months	Assessment of quality of life
5	12 months	Assessment of recurrence and quality of life
	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.

ABPI: 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.27 For inclusion in the study, this reading must have been obtained in the last three months as readings change over time.[28]

Health-related quality of life questionnaires: Short Form Health Survey (SF-12) and 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 three and six 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 one month, three 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 one 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 six, nine 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-12[31] and the EQ-5D.[25] The SF-12 is a reliable and well-validated questionnaire,[32] and has been used in UK populations including with older people and leg ulcer patients.[33,34] 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 3,395 members of the UK public.[35] The EQ-5D has been validated in the UK. The quality of life questionnaires will be administered to patients by postal survey. The EQ-5D will be administered at baseline, 3, six, 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 coordinator within 24 hours and reported to both the trial sponsor and MREC (as per EN 540).[36]

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 it's 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 Clinical Research Nurses 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 competition of questionnaires can drop as patients progress through the trial. However, recent evidence from Edwards *et al* (2002)[37] 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 (0.5W/cm^2) ultrasound, 1MHz, with a pulsed pattern of 1:4. The ultrasound will be applied to peri-ulcer 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 4 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 Clinical Research Nurses 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 (CRNs) 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 less than 5cm^2 will receive 5 minutes ultrasound, those of 10 cm^2 or greater than 10cm^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 (6cm^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 Limited, the largest UK manufacturer of ultrasound machines. Their EMS 3551 machine delivers only 1MHz 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 (+/- 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 five 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 endpoint 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[8] and Vowden[9] found that 60% of ulcers > 10cm^2, and 60% of ulcers of greater than 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 seven weeks (a 32% reduction in healing time, from, 22 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 1.

Table 1. 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**	**7**	**47 (30%)**	**228**	**306**
22 weeks	15.5	6.5	45 (29%)	**274**	366
22 weeks	16	6	42 (27%)	**332**	444
24 weeks	15.5	8.5	59 (35%)	**344**	460
24 weeks	16	8	56 (33%)	**288**	384
24 weeks	16.5	7.5	52 (31%)	**242**	**326**
26 weeks	18	8	56 (31%)	**256**	**344**
26 weeks	19	7	49 (27%)	**354**	476
26 weeks	20	6	42 (23%)	510	682

(calculated using Power and Precision sample size program – 52 week accrual and 52 week additional follow-up)

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 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 coordinating 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 clinical research nurse 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 clinical research nurses. 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 3 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

European Quality of Life Questionnaire (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 vs. 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 method[26] 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% confidence interval 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.[38] A Study Management Committee will be established to oversee the conduct of this trial. The committee will consist of the study coordinator 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 six 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 six 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 three years to complete, with 18 months recruitment and 12-months follow up.

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 coordination and research nurse posts
1-2 Months prior to trial start		Interview and appoint trial coordination and research nurse posts
Uplift Grant Months 1-2		Apply for LREC. Trial coordinator will develop study materials and training materials for clinical research nurses (CRNs)
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 will be responsible for the day to day running of the trial. S/he will help recruit clinical research nurses in each site, provide training (with clinical research nurses - CRNs) to all community and hospital nurses involved in recruiting to the trial; draft six monthly reports to HTA; compile newsletters for clinical sites; liaise with 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) will be the initial point of contact for CRNs, collaborators and all external queries regarding the trial. S/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 (CRNs). 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 quality of life data. S/he will be responsible for generating reminders for nurses / patients to complete the quality of life data (every three months), will receive and log all completed clinical, quality of life 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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