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VenUS IV (Venous leg Ulcer Study IV): A randomised controlled trial of compression hosiery versus compression bandaging in the treatment of venous leg ulcers

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1. Background

1.1 Venous leg ulcers

Venous leg ulcers are one of the most prevalent chronic wound types in the UK, with an estimated point prevalence of 0.16% [1]. However, the occurrence of venous leg ulcers increases with age and the annual UK prevalence in those over 65 years is estimated at 1.7% [2]. Venous leg ulcers develop as the result of underlying venous disease and usually take months to heal. Venous leg ulcers can be painful, malodorous and have been shown to severely impact on patients' mobility and quality of life [3 4]. In severe cases ulceration can result in limb amputation; ulcers are also prone to bacterial infection, including with methicillin resistant Staphylococcus aureus (MRSA).

Venous leg ulcers are costly. In 2004, the Healthcare Commission estimated annual NHS leg ulcer treatment costs of £300-600 million. Recent studies have estimated the annual cost of treating a venous leg ulcer patient to be approximately £700-900; this cost increases as ulcers become larger and longer in duration [5 6]. In the UK, the majority of leg ulcer patients are treated in the community [7], and often make up a large proportion of community nursing caseloads [8]. Community nursing time, particularly that associated with frequent home visits, drives these high costs [6 9]. The increasing proportion of elderly in the population is likely to lead to an increase in the absolute numbers of leg ulcers and consequently costs.

1.2 Compression hosiery

High compression bandage systems (e.g. 4-layer and short stretch) are an effective treatment for venous leg ulcers [10-12], recommended by major UK clinical guidelines for first line use [13 14]. However good clinical outcomes from bandaging (in terms of ulcer healing) rely heavily on nurses' application skills and patient compliance in wearing compression continuously. Further problems with bandaging also exist. Even expertly applied bandages slip and require re-application; the bandages limit patients' ability to self care and bandage bulk can reduce mobility and make wearing shoes difficult. Compression hosiery (in the form of stockings), whilst traditionally used to prevent re-ulceration, is increasingly being used to heal ulcers. As a health technology hosiery has several potential advantages over bandaging: its performance is less likely to be influenced by applicator skill; many patients can remove and re-apply the stockings themselves; and as stockings are less bulky they are easier to wear with shoes and may enhance leg mobility, all of which could improve compliance. Further benefits may be the need for fewer nurse home visits and the re-usability of stockings compared with the disposable bandages. Compression hosiery, for the treatment of venous leg ulcers, comprises two stockings normally worn simultaneously, which last for up to 100 washes. The first stocking provides light to medium compression (10-20 mmHg). A second overstocking provides an additional 20-30 mmHg of compression; totalling 30-40mmHg as with compression bandages.

Reported healing rates with compression bandages vary widely. For example, rates varied significantly between centres in a large RCT after adjustment for important predictors of healing: bandage type, patient mobility, and baseline ulcer area and duration (VenUS I, unpublished data). There is evidence to suggest that bandager skill varies considerably between nurses [15] and that patients often do not like wearing bandages [16 17]. If compression hosiery, which is currently available on prescription, does standardise the delivery of compression and/or improve compliance it may increase ulcer healing rates and be cost-effective. However a pragmatic trial is required; stockings may not yield improvements if patients remove and do not reapply them and/or the compression delivered does not endure sufficiently after washing and reapplying for several months.

1.3 Previous randomised controlled trials of compression bandaging vs. compression hosiery

We have conducted a thorough search for trials comparing compression bandaging with compression hosiery for healing. We identified three trials, all with a follow-up period of 12 weeks [18-20]. An Italian trial [20] compared compression hosiery (Surepress, ConvaTec) with short stretch bandaging. In total, 56 patients with venous leg ulcers were recruited to the trial. After the 12 week study period 44% (12/27) of ulcers healed in the hosiery group compared with 17% (5/29) in the bandage arm ($p = 0.03$). The second trial [18] compared compression hosiery (Venotrain ulcertec) with short stretch bandaging in 134 German venous leg ulcers patients, with blinded outcome assessment of healing. In total, 48% (29/61) of ulcers healed in the hosiery arm, compared with 32% (19/60) in the bandage arm (one sided $p = 0.01$). The final trial [19] (quasi-randomised) involved 50 patients allocated between compression hosiery (Thrombo + Sigvaris) and short stretch bandaging. The authors report that after 12 weeks, 84% (21/25) of ulcers healed in the hosiery group, compared with 52% (13/25) in the bandage arm ($p = <0.05$, actual figure not supplied). Meta-analysis of these trials, excluding the quasi randomised trial, produced a pooled relative risk (RR) of healing of 1.7 ($p = 0.009$; 95% CIs 1.1 to 2.6) in favour of hosiery. Inclusion of the quasi randomised trial also gave a pooled RR of 1.7 (95% CIs 1.2 to 2.3).

Whilst these data suggest that compression hosiery may be an effective treatment in terms of healing venous leg ulcers, the conclusion is based on two small, privately funded trials with short-term follow-up and limited analyses. Further research is also needed in the UK context, using the UK standard 4-layer high compression bandage as a comparator. Additionally, there have been no economic evaluations of the compression hosiery.

2. Research objectives

2.1 Primary objective

To assess the clinical and cost effectiveness of compression hosiery compared with 4-layer compression bandaging in terms of ulcer healing; quality of life and patient concordance.

3. Design

A multi centred, pragmatic, two-armed, parallel randomised controlled trial with equal randomisation.

4. Sample size and recruitment

These sample size calculations are based on VenUS I [12], which recruited 386 participants over 20 months from 9 UK sites. The primary outcome was time to healing. The hazard ratio was 1.33 (95% CI 1.05 to 1.67). The median survival times were 92 days for the 4-layer bandage group and 126 days for short stretch bandage (difference of 34 days). For VenUS IV the primary clinical outcome variable will also be time to healing which is more informative than the commonly used "% of ulcers completely healed" at an arbitrary time point. Our aim is to estimate the size of the difference between the compression systems, rather than to look for a difference of any given size hence we expect that a trial with a total of 400 participants will enable us to estimate the hazard ratio to within 25%, as in VenUS I, where the upper confidence limit, 1.67, is a 25% increase in the point estimate, 1.33. Power calculations suggest that with 400 participants, a median survival in the control group of 100 days and follow-up of one year would provide 90% power to detect an increase in median time to healing of 41 days and a decrease in the hazard ratio for healing to 0.72, or a decrease in median time to healing of 72 days and an increase in the hazard ratio to 1.42. These differences are considerably smaller than the RR of 1.7 found in existing trials. Assuming 10% attrition means 444 participants are required.

However, this sample size calculation is based on the original VenUS I analysis which treated centre as a fixed effect, after checking for a centre by treatment interaction, which was not significant. We have repeated this analysis using robust standard errors to allow for centre as a cluster, hence as a random effect. As might be expected, this inflates the variance compared to a fixed effects model. If we use log area of the original ulcer as a covariate and mobility as a three level factor, then the standard error of the log hazard ratio for the treatment effect is 0.119 if we use centre as a fixed effect. If we use centre as a cluster, hence as a random effect, the standard error is 0.129. This makes the treatment effect not significant (P=0.07). The square of the ratio of these standard errors is 1.19, so this is the ratio in which we think we should increase the sample size to give the same power.

In VenUS 1 there were good reasons to suspect that there would be variation in bandaging skill. Some centres had prior experience using the short stretch bandage control treatment and some did not, some had prior experience in using the 4-layer bandage intervention and some did not.

It is noticeable in the VenUS 1 data that the four centres which showed an advantage to the short stretch bandage were the four smallest. In VenUS IV, the point of the intervention, stockings, is that skill is not required. Any variation in skill will be in the application of the 4-layer bandage which is the control treatment. This is now the standard treatment and all centres should be experienced in its use. We therefore expect that there will be much less variation between centres than in VenUS 1.

The final VenUS IV analyses will look for centre effects and adjust for them using robust standard errors. To allow for the loss of power which this will produce, we need to inflate the sample size by 10% to 489 patients. This extra number is less than the 19% which we would need if the centre effects were like those of Venus 1, but we expect the centre effects in VenUS IV to be much smaller for the reasons given above.

The target of 489 participants translates to a recruitment target of 29 participants per month. We anticipate that we will have at least 12 active centres in the trial including (Western Trust, Bournemouth PCT, Bolton PCT, Leeds PCT and North Yorkshire PCT). The wide inclusion criteria and proposed number of sites will facilitate recruitment and we estimate that each site will be able to recruit 2–3 participants a month. Table 1 shows how we anticipate recruitment will proceed. Recruitment is staggered as some sites will be ready before others depending on local approval processes. We will continue to search for potential sites throughout the trial.

Table 1: Planned recruitment

Months of funding (Post MREC)	Number of sites recruiting	Monthly recruitment targets
1	0	0
2	0	0
3	0	0
4	3	9
5	6	18
6	8	24
7	10	30
8	12	39
9	12	39
10–20	12	30
Follow-up	-	Total: 489

Extension to planned recruitment

We plan to extend the recruitment period. We now anticipate at least 19 trial sites will be actively recruiting from month 13 of the study (October 2010). If each site recruits 1.5 participants per month, the final target of 489 participants would be achieved by October 2011 (Table 2) which is 8 months after planned recruitment was due to end. As shown in the timetable (Appendix 1, page 27), the follow-up period will remain unchanged and will still commence on the 1st of March 2011 and finish 29th February 2012. The period of follow-up will therefore be less for participants who are recruited towards the end of the proposed extended recruitment period. However, we

are confident that the proposed increase in recruitment time and potential decrease in follow-up time (for some participants) have a limited impact on the statistical power of the trial, as described in Appendix 2 (page 29).

Table 2: Extension to planned recruitment

Study month (month post NRES)	Month and year	Target number of sites recruiting	Monthly cumulative recruitment target (*n* participants)
13	Oct 2010	19	154.5
14	Nov 2010	19	183
15	Dec 2010	19	211.5
16	Jan 2011	19	240
17	Feb 2011	19	268.5
18	Mar 2011	19	297
19	Apr 2011	19	325.5
20	May 2011	19	354
21	Jun 2011	19	382.5
22	July 2011	19	411
23	Aug 2011	19	439.5
24	Sept 2011	19	468
25	Oct 2011	19	489

Revised extension to planned recruitment

In order to achieve the original target sample size the recruitment period requires an extra four months. We estimate having recruited 398 participants by the end of October 2011; the additional four months giving us 4 x 23* participants = 92 participants giving an overall estimated total of 490, as shown in Table 3. The recruitment period has therefore been revised as follows: Recruitment will end 29/02/2012, participant follow-up period will end 30/06/2012 and the trial will finish 31/10/2012.

** 23 being the mean number of patients recruited per month between January 2011 to May 2011).*

Table 3: Current and projected recruitment compared to cumulative monthly target recruitment. (as of 31/07/2011):

Month and year	Current recruitment	Projected recruitment (23* pts recruited per month)	Cumulative monthly target recruitment
Jul 2011	329	-	411
Aug 2011	-	352	440
Sep 2011	-	375	468
Oct 2011	-	398	489
Nov 2011	-	421	489
Dec 2011	-	444	489
Jan 2012	-	467	489
Feb 2012	-	490	489

* 23 being the mean number of participants recruited per month Jan 2011 to May 2011).

5. Identification of potential participants

This trial aims to recruit participants with venous leg ulcers. Participants can be recruited from: hospital wards, out-patient clinics, community clinics, GP practice visits, domestic visits and nursing/residential homes. All potential participants will be screened for eligibility by nurses according to the inclusion/exclusion criteria given below.

6. Obtaining informed consent

Participants will be recruited by research nurses, or other recruiting nurses who have undergone the training required for trial participation. Eligible participants will be provided with full verbal and written details of the trial and what participation will involve. Full written consent will be obtained prior to randomisation.

7. Assessment of eligibility

7. 1 Inclusion criteria

Patient has at least one venous leg ulcer[1]

Patient has an ankle brachial pressure index (ABPI) ≥ 0. 8 (taken within last 3 months)

Patient is able and willing to tolerate high compression

Patient is aged ≥ 18 years

[1]*For the purpose of this study a venous leg ulcer will be considered as any break in the skin on the leg* 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 clinically no other aetiology is suspected. Clinical history must be considered and the study participant must have an ABPI of equal to or greater than 0.8. The ulcer must also be venous in appearance (i.e. moist, shallow, irregular shape, venous eczema, ankle oedema).*

*The venous leg ulcer must lie wholly or partially within the gaiter region (as shown in Diagram 1); venous leg ulcers which lie partially within the gaiter region and also extend onto the foot are permitted, however, venous leg ulcers which are confined to the foot only are NOT permitted for inclusion within this trial.

7.2 Exclusion criteria

Patient has an ABPI greater than 1.20 (taken in last 3 months), and in the nurses clinical judgement and/or according to local guidelines, patient should not receive high compression[2]

Leg ulcer of non-venous aetiology (i.e. arterial)

Wound exudate levels too high for the use of compression hosiery (nurse judgement[3])

Patients are unable or do not wish to consent to participation in the trial

Patients are currently in another study evaluating treatments for their leg ulcer

Known allergy to any trial product

Patient has previously been in this trial

Patient has gross leg oedema

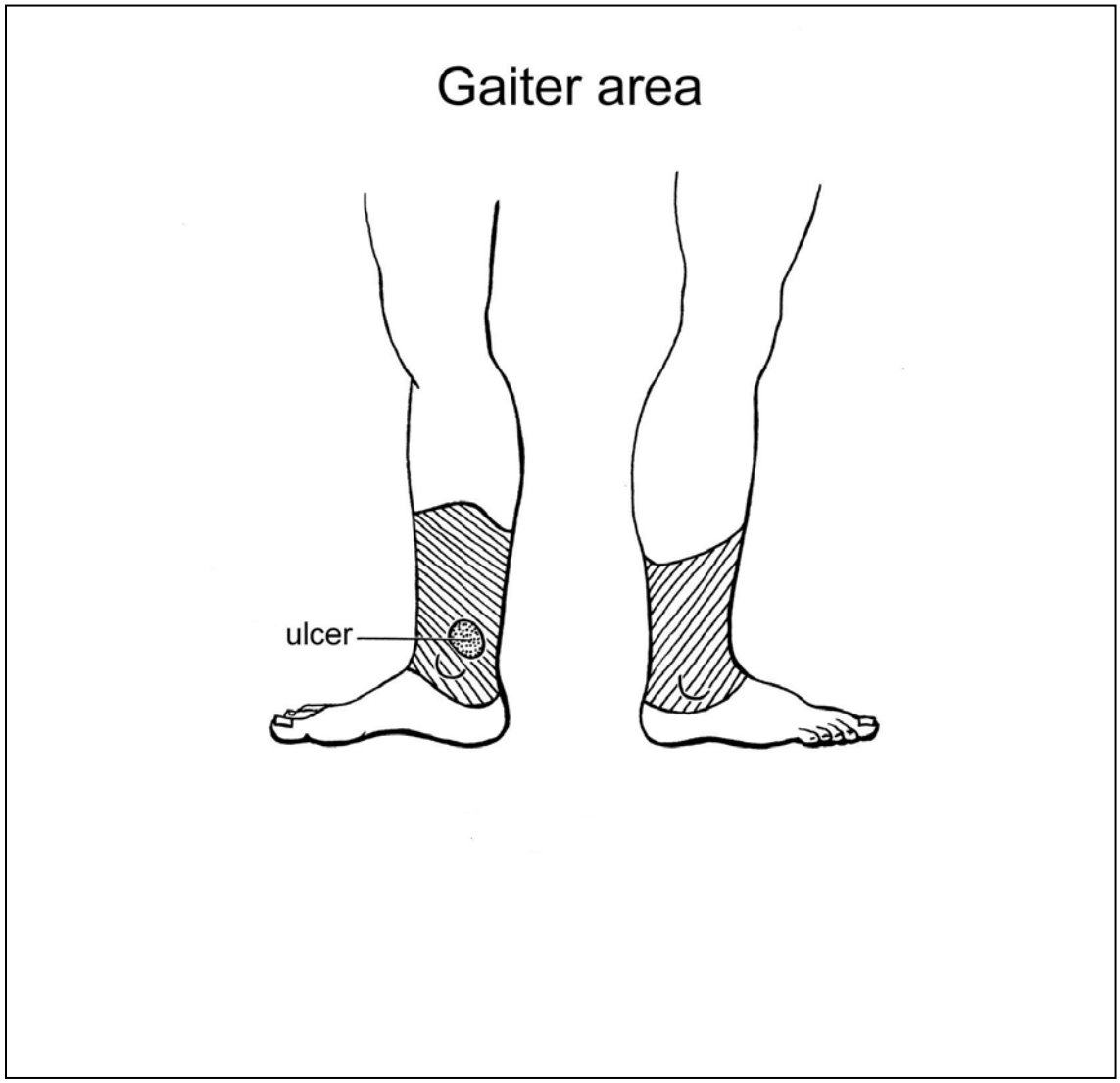
Other reason (nurse judgement)[4]

[2]Where the patient has an ABPI greater than 1.20, the decision regarding the appropriateness of a high compression treatment, thus the exclusion of the patient from the trial is dependent on local guidelines and clinical judgement.

[3]We rely on nurse judgement regarding exudate levels. Previous VenUS trials have highlighted that it is very difficult to make an explicit statement regarding how much exudate is too much so as to prohibit the use of a treatment. Thus, pragmatically, we rely on nurses clinical judgement as to whether a leg is too 'wet' for inclusion, i.e. exudate levels are so high that compression hosiery would not be deemed suitable. If high exudate levels are the sole reason for exclusion, a patient will be re-considered for inclusion once exudate has been managed.

If, in the clinical judgement of the nurse, the patient is not suitable to take part in the trial, please record the reason here.

Diagram 1: The gaiter region (From Maggisano and Harrison[21])



People who do not speak/understand English are eligible to participate in this RCT provided they are able to give informed consent. Local NHS-based translation services will be used where available. We plan to use only English language health-related quality of life instruments. Participants unable to complete these tools will be followed up for healing/compliance data only.

Our experiences from previous trials suggest this will only apply to a small number of people. If this is not the case we will investigate the use of translated instruments as required. Translated instruments used must have evidence of cross-cultural validation.

7.3. Definition of reference ulcer and reference leg

Where a participant has multiple venous ulcers, the eligible ulcer with the largest surface area (cm^2) will be termed the **reference ulcer** and will be followed to determine time to healing of the reference ulcer.

The leg on which the reference ulcer is located will be termed the **reference leg.** Where participants have bilateral leg ulcers we will assume that the leg with the reference ulcer is the leg with the worst prognosis.

8. Randomisation

Randomisation will be conducted via a remote telephone randomisation service (free phone) based at the University of York. If convenient, web-based randomisation will also be available (http://www.yorkrand.com/). Randomisation will be conducted using a pre-validated computer programme, ensuring complete allocation concealment. Randomisation will be stratified by ulcer duration (≤ 6 months and more than 6 months) and ulcer area (≤ $5cm^2$ and more than $5cm^2$) using permuted blocks: these variables are known predictors of healing. Once randomised, participants will begin their trial treatment immediately. At randomisation participants will be given a unique identification number to be used for identification purposes throughout the trial.

9. Baseline assessment

Baseline data will be collected from all consenting participants prior to randomisation. Data collected will include:

- Participants name and address, and, if used by the participant, mobile telephone number and email address (for the receipt of follow-up questionnaires), date of birth and centre in which the patient is located
- Details of participant's GPs
- A tracing of the reference ulcer(s) and all other ulcers on the reference leg using a wound grid and a fine-nibbed marker pen. All ulcers on the leg will be drawn on to a leg-diagram and the reference ulcer clearly labelled.
- A digital photograph of the reference ulcer and the reference leg.
- History including: diabetic status, duration of the reference ulcer, previous ulcer episodes, weight and height and level of mobility
- ABPI reading using an established technique (or record of an assessment carried out within the last 3 months)

- Ulcer-related pain
- Establishment of participant treatment preference (i.e., indifferent to treatment allocation, prefer 4-layer compression bandaging, prefer compression hosiery).
- Ankle circumference

10. Trial treatments

10.1 4-layer compression bandaging (4LB)

Control arm participants will receive 4-layer compression bandaging (4LB); this is an effective treatment for venous leg ulcers, recommended by major UK clinical guidelines for first line use. 4LB has been selected over the short stretch bandage as it is the most commonly used high compression system in the UK and we have evidence from the VenUS I trial and from an individual patient data meta-analysis of RCTs [22] that 4LB significantly reduces time to healing compared with short stretch bandaging. Details of a 4LB system are presented below (Table 2). We will not specify a specific kit or series of products for use, but allow nurses to use their normal 4-layer system as long as they are designed to deliver 35-40 mmHg at the ankle and fit the criteria outlined in Table 2a with examples (not exhaustive) of each bandage type listed in Table 2b. The system used will be recorded. Standard application procedures will apply. We do not anticipate that nurses will require training in the application of 4LB as it is a usual treatment. However, if there is a training need this will be met by the local research nurse.

Table 2a: Recommended high compression 4-layer system (40 mmHg compression at the ankle). NB: Measure the circumference of the ankle at the narrowest point.

Ankle circumference	Layer 1	Layer 2	Layer 3	Layer 4
<18cm	Wool to make circ min. 18cm	Crepe bandage	Class 3a bandage	Cohesive bandage Class 3b
18–25cm	Wool	Crepe bandage	Class 3a bandage	Cohesive bandage Class 3b
25–30cm	Wool	Class 3c bandage	Cohesive bandage	
>30cm	Wool	Class 3a bandage	Class 3c bandage	Cohesive bandage Class 3b

Table 2b: Examples of bandage type

Wool	K-Soft® (Urgo) Profore® #1 (S&N Hlth.)
Light support bandage	K-Lite® (Urgo) Profore® #2 (S&N Hlth.)
Class 3a bandage	K-Plus (Urgo) K-Plus® Long (Urgo) Profore® #3 (S&N Hlth.) Elset®, (Medlock) CliniPlus (Clinisupplies)
Class 3b bandage	Ko-Flex®, ®(Urgo) Profore® #4(S&N Hlth.) Coban®(3M) Ultra Fast®(Robinsons)
Class 3c bandage	MedlockSetopress® (Medlock) Tensopress® (S&N Hlth) Profore+® S&N Hlth

10.2 Compression hosiery

The intervention being compared with standard care is compression hosiery delivering high levels of compression. Such products are available in the UK, and are on FP10. We will evaluate the current systems of compression hosiery that consist of a two layer compression stocking system delivering sustained, graduated compression of 40mmHg at the ankle. All current systems that meet these criteria are detailed in Table 3. The first layer is an understocking or liner providing light compression over which a second overstocking (i.e. UK class 2 or 3 depending on the understocking) can easily slip. Any new compression hosiery systems introduced during the trial will be considered on a case by case basis for inclusion into the trial.

Table 3: Compression hosiery kits

	Understocking (mmHg)	**Overstocking (mmHg)**	**Self-applicator**	**FP-10**	**Custom service for very large legs**
Mediven Ulcer system	20	20	YES: Actiglide to help overstocking slide over understocking.	Yes	Yes
Activa – leg ulcer hosiery kit	10	25-35 (class III)	YES: Easy-on slipper to help overstocking slide over understocking.	Yes	Yes
Jobst UlcerCARE	10	30	YES: Over-stocking with a zip at the rear.	Yes	Yes
Venotrain® ulcertec	10	30	YES: Glider	Yes	No

As with bandaging, the size of stocking used depends on the leg size and product-specific measurement tables will be used to select the appropriate stocking based on ankle circumference (and/or calf circumference). Where applicable, made to measure stockings may be required. If the treating nurse feels it is appropriate, the participant may be told that they can remove the overstocking during the night and reapply it in the morning as long as they are sleeping in bed with the legs elevated.

All trial nurses are likely to have received training in the use of compression hosiery. However, refresher training will be organised with the relevant manufacturer if required. We will also ensure that all community nurses treating trial participants are trained in the application of compression hosiery and the management of patients receiving this treatment. All participants will be given a minimum of two stockings sets — one to wash and one to wear. Stockings will be replaced in line with manufacturer recommendations but can be replaced sooner if deemed necessary by the treating nurse, this will be recorded. The potential of the compression hosiery to reduce nurse time compared with bandaging is an important feature of this trial. Any positive

or negative impact of this will be evaluated indirectly through the outcomes being collected (time to healing, health related quality of life and resource use).

If a participant stops receiving the trial treatment, the reason will be recorded as will their new (non-trial) treatment.

11. Primary contact layer

Nurses will be able to use any primary contact dressings of their choice under the bandaging or dressing. Dressings used will be recorded by type.

12. Trial follow-up

Following randomisation trial nurses will record every visit to the participant using a visit pro-forma. All visits will be recorded until the participant's reference leg is ulcer free and no more nurse visits are required to treat this leg or until the participant exits the trial; the maximum period for trial follow-up is 12 months following randomisation.

Health related quality of life data/self reported resource use will be collected at baseline and then at 3, 6, 9 and 12 months. Multiple follow-up periods allow for changes in health-related quality of life to be assessed accurately and facilitate recall of events for self-reported resource use. Furthermore, follow-up of healing over this period means that more healing events are likely to occur, ensuring that median time to healing can be reported, as well as having a reasonable timeframe in which to assess recurrence.

13. Outcomes

13.1 Primary outcome measure (nurse report and images for blinded outcome assessment)

The primary outcome of this trial is time to healing of the reference ulcer, defined as: complete epithelial cover in the absence of a scab (eschar) with no dressing required.

Treating nurses will document the date they class the reference ulcer as healed. They will be asked to telephone the York Trials Unit Randomisation line to report the date when they consider the reference ulcer and the reference leg has healed. Additionally, data on the reference ulcer will be collected throughout the study in the form of digital images. A digital image will be taken at baseline and monthly thereafter. A digital image of the wound will then be taken when the treating nurse records the reference ulcer as healed. After this point images will be taken once a week over the next 4 weeks. These images will be assessed by two blinded clinical experts to decide a blinded date of healing, with disagreements being resolved through discussion and the involvement of a third reviewer if required. The blinded assessment of healing date will be used as the primary healing endpoint. Non-blinded assessment of healing will be used as a secondary outcome.

13.2 Secondary outcome measures

13.2.1 Resource use (for cost utility and cost effectiveness analysis based on time to healing of patient)

Resources used by nurses will be collected until healing of the reference leg with no more nurse visits required, or until trial exit using the simple visit proforma which will be completed at each treatment visit. This form will record details of the treatment given to the participant (e.g. compression system applied, dressing type used under the bandage/stocking). The date of each visit will be recorded and in this way the number of nurse visits calculated. We will also collect data from the nurses on inpatient stays (e.g. surgical treatment of ulcer). Furthermore, participants will be asked (along with health related quality of life information discussed below) whether they are using other services, such as GPs, because of their ulcer. At three monthly intervals they will also be asked if they are ulcer-free. For the assessment of incremental costs and Quality Adjusted Life Years (QALYs) it is important to know if participants' are alive at the end of the trial. Where people are ulcer-free this on-going monitoring is particularly important as the nurses will stop treating the participant. Local research nurses will be contacted monthly to notify York Trials Unit if any trial participants have died during this period. To ensure we have this information at the end of the trial if a nurse is unsure about the status of a healed participant, we will contact the participant's GPs, offering a per patient payment for this information.

13.2.2 Time to ulcer-free reference leg

Although the clinical analysis defined the primary outcome based on healing of the reference ulcer, the clinically relevant outcome is healing of all ulcers (ulcer free patient). We will assume that the reference leg is independent of the non-reference leg (even if this has ulcers), and that healing of the reference leg is the main outcome for evaluation in the economic analysis.

13.2.3 Health related quality of life (collected at baseline then via postal survey at three monthly intervals (baseline, 3, 6, 9, and 12 months)

Health related quality of life will be assessed using generic measures, the SF-12 (version 2, **standard recall)** and the European Quality of Life questionnaire (EQ-5D) and an ulcer-related pain scale.

The SF-12 has been well-validated in a variety of UK populations including older people and leg ulcer patients [23 24]. It measures 8 domains which can be used to
calculate summary physical and mental component scores.

The EQ-5D questionnaire is a widely recognised and validated generic measure of health related quality of life. This questionnaire has been assessed for acceptability and validity in patients with venous leg ulcers [23 25-27] as well as being validated in a number of other patient groups [28-36].

Individual's EQ-5D values will be used to calculate their specific QALYs at 12 months using the area the under curve method. The use of QALYs is widely recognised and is the measure of

health benefit used by NICE. Work carried out by the applicants has shown that both measures are able to measure health related quality of life in those with venous leg ulcers [23].

A systematic review investigating ways of increasing questionnaire response rates [37] reported that response to postal questionnaires was doubled (OR = 2.02; 95% confidence intervals 1.79 to 2.27) when a financial reward was included with the questionnaire, versus no incentive. The response rate increased further when the incentive was not conditional on response, versus upon return of questionnaire (OR = 1.71; 95% confidence intervals 1.29 to 2.26). Based on these data we will include £5 with the final questionnaire sent to participants at 12 months. In their 9 month letter participants will be told of this unconditional token of our appreciation for the time they have taken to complete documentation*. This approach has been used successfully in VenUS II and III. We will also investigate the use of electronic reminders.

*There will be some participants who are recruited later into the trial and therefore will not be followed up for 12 months and subsequently will not receive a 12-month questionnaire. For example, any participant recruited in February 2012 can only be followed up for a maximum of four months until the end of the follow-up period (30/06/2012). Participants who are not followed-up for the full 12 months will instead receive £5 with their final questionnaire.

13.2.4 Patient concordance to treatment (throughout trial)

To monitor on-going use of treatment nurses will be asked to record change from the trial treatment to another treatment and the reason for this change. This includes whether the change from trial treatment was requested by the patient or based on a clinical decision.

We also want to investigate participants' views on compression hosiery and 4LB. We will ask participants to complete a questionnaire one month after randomisation. Participants allocated to wearing compression hosiery will be asked how often they wear hosiery for, how many layers they wear and whether they or a carer apply the hosiery. We will ask participants allocated to wearing 4LB how often they wear the bandages and if they have ever removed any bandage layers. Participants will also be asked an additional question regarding the acceptability of the treatment in terms of comfort. We will also include an open-ended section for people to use their own words to describe their views on their treatment if they wish to.

13.2.4 Recurrence

Before high compression hosiery was developed, compression hosiery was used as a low-compression 'maintenance' treatment to prevent ulcer recurrence. We would like to investigate whether those who become used to wearing the hosiery and heal are also more likely to wear maintenance hosiery after healing. Reduction in recurrence would help reduce the prevalence of this condition and thus cost.

We will ask nurses on a monthly basis to record if there has been recurrence of a venous leg ulcer on the reference leg post-healing. This part of the study will be exploratory as it is likely to have low power.

To check that as many recurrence events are being recorded as possible, we will also give participants with a healed reference leg a reference leg-specific postcard and pre-addressed and postage paid envelope. This postcard can then be returned to the York Trials Unit if participants want to report an ulcer recurrence. If we receive such a postcard the local research nurse will be contacted to confirm the event.

13.2.5 Adverse events (throughout trial)

These will be recorded following good practice guidelines and Trials Unit standard operating procedures. **See Section 17.**

14. Trial exit

Participants will exit the trial completely if:

- they have been in the trial 12 months following randomisation
- they request to/are unable to continue being followed-up
- they are lost to follow up
- they die

15. Trial analysis

15.1 Primary outcome

The primary outcome will be time to healing. The primary analysis will be on an 'intention-to-treat' basis and will compare the median time to complete healing (of the reference ulcer) between the trial arms. Kaplan-Meier survival curves will be constructed for each group. For the primary analysis a p value smaller than 0.05 for two tailed tests will be taken to indicate statistical significance.

Randomisation should lead to balance in prognostic factors. Nevertheless, an adjusted analysis will be undertaken as this will generally result in better precision (i.e., smaller confidence intervals) than an unadjusted analysis [38 39]. A Cox regression model will be fitted to the data to test for any differences between the two groups. The two stratification variables, size and duration of the ulcer, will be included. In addition to the stratification variables centre effects will be adjusted for using robust standard errors. We will present an unadjusted analysis; however, the adjusted analysis will have primacy. We will also present a CACE analysis [40-43], secondary to the intention to treat analysis to account for compliance.

15.2 Secondary outcomes

15.2.1 Economic Evaluation

The cost effectiveness of compression hosiery versus 4LB in the treatment of venous leg ulcers will be explored in a cost-effectiveness and a cost-utility analysis. The perspective for both analyses will be that of the UK NHS and Personal Social Service [44]. The cost-effectiveness approach will assess value for money in terms of ulcer healing, and the cost utility analysis will assess cost per life year gained. The use of a generic outcome is important to decision makers, who must compare cost versus benefit across many disease areas.

Health benefits associated with high compression stockings and 4LB will be measured in terms of both estimates of the mean time to healing after 12 months, and mean QALYs. The EQ-5D will be used to elicit patient utility values at different points in time and used to calculate QALYs for each patient using the area under the curve. These utility values will then be used to 'quality adjust' each patient's survival time.

Mean within trial estimates of cost and health benefits will be estimated using the regression approach to allow for the correlation between costs and effects as well as adjusting for covariates. This analysis will also account for skewness and censoring associated with time to event and cost data [45-47].

There is increasing awareness that the findings from any RCT should not be considered in isolation but, in fact, are more valuable when used to update existing evidence on all treatments of interest. Thus as well as conducting the trial-level analysis, we propose a second analysis to assess the cost-effectiveness high compression devices, which will incorporate the findings from VenUS IV. To identify all existing evidence we will update a systematic review [11] of the clinical and economic literature on the effectiveness and cost-effectiveness of high compression in the treatment of venous leg ulcers [48]. Estimates of clinical effectiveness previously reported in the literature and those estimated in VenUS IV will be used to construct a network of evidence describing existing head to head comparisons between alternative high compression systems in the treatment of venous leg ulcers [49]. Bayesian statistical methods will be applied to this network of evidence in order to explore the relative effectiveness of existing compression systems with respect to each other [49]. In order to accommodate the existence of different information sources, a comprehensive decision analytic model will be constructed [50].

The uncertainty surrounding the decision to accept a high compression treatment as the most cost-effective will be explored in cost effectiveness acceptability curves [51]. These curves depict the probability of accepting a treatment as being cost-effective for a large range of willingness to pay values for an extra unit of health benefit. Acceptability curves for all treatments will then be simultaneously compared to define the cost-effectiveness acceptability frontier for the same range of willingness to pay values used before. This in turn will allows to identify the high

compression treatment associated with the highest probability of being cost effective for a range of willingness to pay values.

15.2.2 Recurrence

Time to ulcer recurrence of the reference leg will be used to construct Kaplan-Meier survival curves for each group.

15.2.3 Other outcomes

Other secondary measures include quality of life measures SF-12 ulcer related pain, (at 3, 6, 9 and 12 months) and patient's views on compression hosiery and 4LB at 1 month. Descriptive statistics will be presented. Where appropriate continuous measures will be analysed using analysis of covariance (using transformation if required) and categorical variables analysed using logistic regression or ordinal regression models.

An adverse event is defined as "any undesirable clinical occurrence in a subject, whether it is considered to be device related or not" [52].

16.0 Sub-study investigating the validity of the VEINES-QOL scale in venous leg ulcer patients.

We will also extend work on health related quality of life (**section 13.2.3**) by collecting data using a disease specific questionnaire. The VEINES-QOL [53 54] is a 26-item questionnaire designed for use in patients with chronic vascular disorders of the leg. Four language versions including English have been developed and evaluated for reliability and validity. These data will be collected at baseline, and two weeks and four months after randomisation.

The VEINES-QOL questionnaire for assessing venous-disease-specific quality of life has good psychometric properties when used with a mixed sample of people with venous leg diseases [54] and in people with deep vein thrombosis [55]. Although venous leg ulcer patients were included in the study of [54], they were only a small part (2%) of the sample and results were not presented for them separately. We would like to know how well VEINES-QOL can measure disease-specific quality of life in patients with venous leg ulcers.

16.1 Design

We will incorporate this sub-study into the VenUS IV trial. We wish to investigate the following aspects of validity: internal consistency, repeatability or test-retest reliability, construct validity, and responsiveness. We propose to add the VEINES-QOL questionnaire to the baseline questionnaire battery. This will enable us to study internal consistency and construct validity. We will give a repeat questionnaire after two weeks to measure the test-retest repeatability. We will give a further questionnaire at 4 months to assess responsiveness. The questionnaires sent at two weeks and four months will be mailed separately from other study questionnaires.

16.2 Rationale for timings

The questionnaire sent at two weeks is intended to provide information on the repeatability of the VEINES-QOL questionnaire. The baseline and two-week questionnaires should be sufficiently far apart for the respondents to the two-week questionnaire to have forgotten their answers to the first questionnaire (at baseline), so that they are not trying to reproduce their original answers. They should be sufficiently close together for the quality of life not to have changed greatly. Two weeks is an interval often used in questionnaire validation and was used by [55].

The third questionnaire, sent at four months, is to provide information on responsiveness. We estimate that about 60% of participants will have healed by four months, based on the VenUS I four layer bandage group [12]. Thus we have a comparison close to the maximum power between healed and non-healed participants.

The two-week and four month questionnaires are sent at times when no other questionnaire data is to be collected. We wanted to avoid giving participants very large questionnaires with many scales. We think that it will be less burdensome to participants and less likely to discourage response if we give several short questionnaires rather than one large one. Also, the VEINES-QOL has similarities with the SF-12 scale which we are using as an outcome measure and we have tried to avoid asking the two together. We cannot avoid this at baseline, because we need to look at the relationship between VEINES-QOL and SF-12.

16.3 Sample size

Most of the analyses will use correlation coefficients. With 400 participants, typical confidence intervals for correlation coefficients would be:

r	95% CI
0.2	0.10 to 0.29
0.4	0.31 to 0.48
0.6	0.53 to 0.66
0.8	0.76 to 0.83

We think that these would be well enough estimated. We could use only a sub-sample for one or more of the questionnaires, as [55] did for test-retest repeatability, but this would increase complexity and lose information, so we think it best to include all participants.

16.4 Information and consent

Participants will be informed at recruitment that we are including a study of a new questionnaire which we hope will tell us more about how venous ulcers affect people's lives. Participants will be asked to consent to this when they consent to the VenUS IV trial.

16.5 Proposed analysis

Internal consistency will be measured by Cronbach's alpha at the baseline. This uses only the items of the VEINES-QOL. We will also estimate correlations between each item and the total

score and the percentage response to each possible answer, to see whether any items should be dropped from the scale.

Construct validity will be measured by correlation with other scales and variables at baseline. We would expect a relationship with other quality of life measures and severity measures such duration and size of ulcer. We expect no relationship with variables unrelated to the ulcer, such as age and sex.

Repeatability will be measured by correlation between the test and retest scores. We will also look at this for individual items using weighted kappa statistics.

Responsiveness will be by estimation of the difference in mean score at four months between participants whose ulcers have healed and those who are unhealed. This will be presented as an effect size in baseline standard deviations and can be compared to the corresponding difference for SF-12 at 3 and at 6 months. The standard errors for these estimates will be after adjustment for the baseline measures.

17.0 Adverse Events

Both treatment-related and unrelated adverse effects will be reported to the trial office on an adverse-event reporting form. The reporting clinician will indicate whether, in their opinion, the event is related to trial treatment, or not. Events will be classified as serious or non-serious. Some events are always classified as serious (death, life threatening risk, hospitalisation, persistent or significant disability/incapacity). For other events the treating nurses will make a clinical decision about the seriousness. Nurses are asked to report serious adverse events, such as admission to hospital directly to the Trial Coordinator.

We have a list of possible treatment-related adverse events a priori, based on reports in the literature and the VenUS I trial. These are described below.

17.1 Pressure damage

Excessively high levels of compression or the inappropriate application of compression can lead to pressure damage and in a small number of cases, leg or foot amputation though frequently these adverse outcomes are not well described in research reports. Pressure damage presents on pressure areas (areas of small radius and/or little padding) such as the malleoli, Achilles tendon, or the front of the foot and is indicated by non-blanching erythema. Bands of high pressure on the leg can result in lines of skin damage along the lines of the bandage. Assessment of the skin of the leg after each bandage removal is a fundamental part of leg ulcer management.

17.2 Maceration, excoriation and infection

Compression bandages may keep wound exudate in contact with the skin surrounding the ulcer, leading to maceration of the peri-ulcer skin. Occlusion of the ulcer and the skin provides a moist environment, which may encourage fungal and bacterial infections of the peri-ulcer skin or the

ulcer itself. Maceration presents as swollen, white, soggy skin. Excoriation is the appearance of red, inflamed skin around the ulcer, thought to be due to wound exudate which contains enzymes. Infection presents usually with a combination of any or all of inflammation, pain, odour, heat and purulent discharge.

17.3 Ulcer related pain

Research investigating the impact of a leg ulcer on quality of life has demonstrated that pain is one of the most troublesome aspects of having a venous leg ulcer.

17.4 Ulcer deterioration

Ulcer deterioration includes an increase in ulcer area, malodour, apparent allergy and ulcer bleeding.

17.5 Expected but unrelated serious adverse events

This is the fourth venous ulcer study (VenUS). The patient populations varied slightly within each trial, with the population of VenUS I being the most similar to the current VenUS IV study. Whilst the expectedness and relatedness of each serious adverse event in VenUS IV will be considered on an individual basis, it is important to note that some serious adverse events are expected in the trial. However, there is no expectation that use of either trial treatment will be related to such events. In VenUS II a total of 49% (131/267) participants reported at least one adverse event, with 14% (47/267) of participants reporting at least one serious adverse event.

The participant population recruited to VenUS IV will be, on average, elderly. In the VenUS I trial the mean age of participants was 71 years and in VenUS II it was 74 years. Additionally, previous research shows that people with venous leg ulceration are likely to have other co-morbidities including: hypertension, congestive heart failure and osteoarthritis[56] Given the age and health status of the likely VenUS IV participant population we would expect to see some treatment-unrelated hospital admission during the trial, both for elective surgery and other reasons. In this population we would also expect the occurrence of other medically important conditions, again, that are not related to treatment. We would also expect to see a small number of deaths. In VenUS I 9% (35/387) of participants died during the study period (up to 580 days follow up). In VenUS II (up to 365 days follow-up) this figure was 3% (9/267).

18. Trial End

Study completion will be defined as completion of the study at all sites. Completion refers to the date of final data collection as described in the protocol. Paper records from the trial will be stored for 5 years from trial end.

19. 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 contribute to the drafting of the final report.

Trial Secretary 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; 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 the York Trials Unit.

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 the 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.

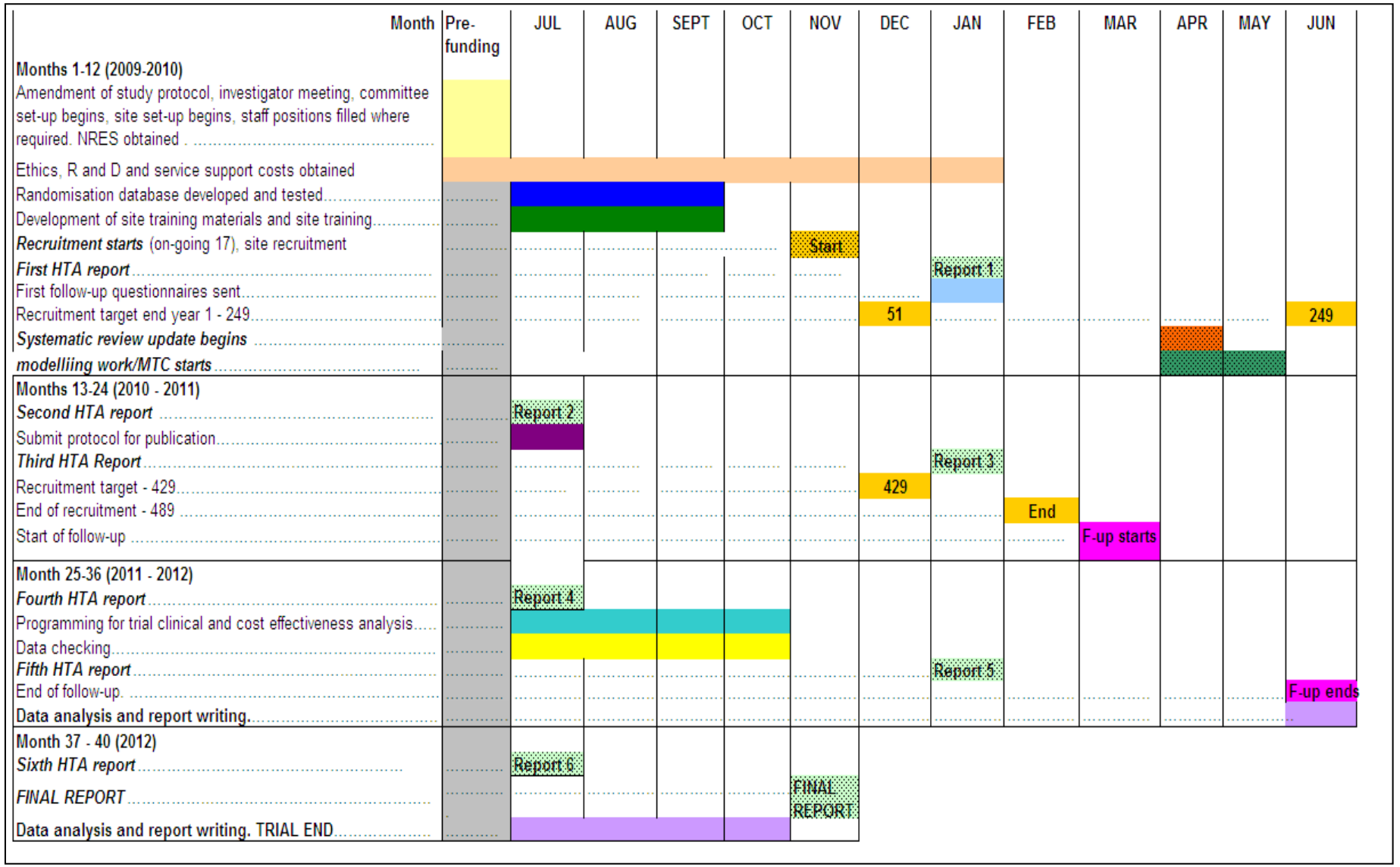
20. Supervision of trial

This trial will be run according to the Medical Research Council (UK) Good Clinical Practice Guidelines. 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 main 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.

Due to the low risk nature of the interventions being assessed, which are both currently used in the NHS, VenUS IV does not plan to have a **Data Safety and Monitoring Committee.** Rather the role will be incorporated in to that of the Trial Steering Committee, pending their agreement.

Appendix 1: Trial Timetable



Appendix 2: Effect of recruiting participants in the final year of the study.

The proposed sample size for VenUS IV is 489 participants to be followed for one year. In survival analysis, what matters for the sample size is the number of events. At one year, the 4 layer bandage arm of VenUS I had a 12 month healing rate = 77%. In VenUS IV we would therefore expect 489×0.77 = 377 healing events. If we shorten the follow-up period at the end of the trial and allow recruitment to continue, would we gain many healing events? Here is the survival function for VenUS I in the four-layer bandage arm, follow-up to one year:

Time (months)	Beginning Total	Heal	Net Lost	Survivor Function
1	195	26	3	0.8667
2	166	39	3	0.6631
3	124	28	2	0.5133
4	94	15	0	0.4314
5	79	11	0	0.3713
6	68	6	3	0.3386
7	59	2	1	0.3271
8	56	4	1	0.3037
9	51	4	1	0.2799
10	46	3	1	0.2617
11	42	2	0	0.2492
12	40	3	37	0.2305

We can estimate the number of healings for any length of follow-up by multiplying the number of months of follow-up by one minus the survivor function. We do this for months 11 down to 4; this gives us a total of 158 events.

Hence continuing to recruit for eight months into the final year of follow-up will give us an estimated extra 158 healing events. This will be true only if the healing rate is as in VenUS I, which it should be, because the patient definition is the same.

Assuming a recruitment rate of 1.5 participants/month for 19 sites, increasing recruitment over eight months means we would recruit 232 extra participants. At a full 12-month follow-up these 232 extra participants would generate 179 events. Thus, reducing follow-up to a minimum of four months means we would miss only 21 events in these participants. (These calculations ignore those lost to follow-up because of death, moving away, etc., but in VenUS I these were few.)

21. Trial sites and local principle investigators

1) Bolton - Jacqui Ashton (PI)

2) Bradford - Kathryn Vowden (PI)

3) Brighton - Terry Shipperley (PI)]

4) Cambridge - Anne-Marie Perrin (PI)

5) Cornwall and Isles of Scilly - Nicci Kimpton (PI)

6) Danetre - Amerdeep Heer (PI)

7) Dereham - Karen Johnson (PI)

8) Diss - Clare Cattermole (PI)

9) Epsom and St Helier - Pauline Beldon (PI)

10) Hainault - Debbie Wickens (PI)

11) Harrogate - Alison Layton (PI)

12) Harrogate GP – Fiona Buckley (PI)

13) Harrogate GP - Rachael Robinson (PI)

14) Harrogate GP – Nick Taylor (PI)

15) Hull - Shernaz Walton (PI)

16) Kent - Sara Kray (PI)

17) Kingston - Wyn Glencross (PI)

18) Lancashire - Nicky Morton (PI)

19) Latham - Amanda Youle (PI)

20) Leeds - Nikki Stubbs (PI)

21) Mid Yorkshire and Wakefield - Leanne Cook (PI)

22) Mowbray (Harrogate) - Stephen Foley (PI)

23) Nantwich – Lalit Gurnani (PI)

24) North Lancashire - Lynn Atcheson (PI)

25) North Yorkshire - Una Adderley (PI)

26) Northern Ireland - Anne Witherow (PI)

27) Northumberland - Val Douglas (PI)

28) Norwich - Julie Lambert (PI)

29) Nottingham - Sarah Pankhurst (PI) (*site withdrawn*)

30) Sedgefield - James Larcombe (PI)

31) South of Tyne and Wear - Jeanette Milne (PI)

32) Sudbury - Amanda Keighley (PI) (*site withdrawn*)

33) Whitby - Martin Linton (PI)

34) York Hospital - Calum Lyon (PI)

22. Membership of TSC

Ian Chetter (chair)

Jenny Freeman (external member)

Brenda King (external member)

Nicky Cullum

Jo Dumville

Rebecca Ashby

Una Adderley

Nikki Stubbs

Jacqui Ashton

Anne Witherow

Jude Watson

Martin Bland

David Torgerson

Cynthia Iglesias

Arthur Kang'ombe

Marta Soares

Shehzad Ali

Gillian Worthy

Sue Collins

Ben Cross

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