Aspirin for Venous Ulcers

Trials

Aspirin for Venous Ulcers: Randomised Trial (AVURT): Study Protocol for a Randomised Controlled Trial

--Manuscript Draft--

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Abstract:	Background: Venous leg ulcers (VLUs) are the commonest cause of leg ulceration, affecting 1 in 100 adults. There is a significant health burden associated with VLUs - it is estimated that the cost of treatment for one ulcer is up to £1300 per year in the NHS. The mainstay of treatment is with graduated compression bandaging, however treatment is often prolonged and up to one quarter of venous leg ulcers do not heal despite standard care. Two previous trials have suggested that low-dose aspirin, as an adjunct to standard care, may hasten healing, but these trials were small and of poor quality. Aspirin is an inexpensive, widely used medication but its safety and efficacy in the treatment of VLUs remains to be established. Methods / design: AVURT is a phase II randomised double blind, parallel-group, placebo-controlled efficacy trial. The primary objective is to examine whether aspirin, in addition to standard care, is effective in patients with chronic VLUs (i.e. over 6 weeks in duration or a history of VLU). Secondary objectives include feasibility and safety of aspirin in this population. A target of 100 participants, identified from community leg ulcer clinics and hospital clinics, will be randomised to receive either 300mg of aspirin once daily or placebo. All participants will receive standard care with compression therapy. The primary outcome will be time to healing of the reference ulcer. Follow-up will occur for a maximum of 27 weeks. The primary analysis will use a Cox proportional hazards model to compare time to healing using the principles of intention to treat. Secondary outcomes will include ulcer size, pain evaluation, compliance and adverse events. Discussion: The AVURT trial will investigate the efficacy and safety of aspirin as a treatment for VLU and will inform on the feasibility of proceeding to a larger phase III study. This study will address the paucity of information currently available regarding aspirin therapy to treat VLU. Trial registration: The study is registered on a public database with clinicaltrials.gov (NCT02333123; registered on 5th November 2014). Key words: Leg ulcer, venous ulcer, wound healing, aspirin, compression therapy
Corresponding Author:	Rachael O Forsythe St George's Vascular Institute UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	St George's Vascular Institute
Corresponding Author's Secondary Institution:	
First Author:	Helen Tilbrook
First Author Secondary Information:	
Order of Authors:	Helen Tilbrook

	Rachael O Forsythe
	Debbie Rolfe
	Laura Clark
	Martin Bland
	Hannah Buckley
	Ian Chetter
	Liz Cook
	Jo Dumville
	Rhian Gabe
	Keith Harding
	Alison Layton
	Ellie Lindsay
	Catriona McDaid
	Christine Moffatt
	Ceri Phillips
	Gerard Stansby
	Peter Vowden
	Laurie Williams
	David Torgerson
	Robert J Hinchliffe
Order of Authors Secondary Information:	
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Authors:

Helen Tilbrook; email: helen.tilbrook@york.ac.uk (1)

Rachael O Forsythe; email: rachael.forsythe@ed.ac.uk (2)

Debbie Rolfe; email: drolfe@sgul.ac.uk (3)

Laura Clark; email: laura.clark@york.ac.uk (1)

Martin Bland; email: martin.bland@york.ac.uk (1)

Hannah Buckley; email: hannah.buckley@york.ac.uk (1)

Ian Chetter; email: ian.chetter@hey.nhs.uk (4)

Liz Cook; email: liz.cook@york.ac.uk (1)

Jo Dumville; email: jo.dumville@manchester.ac.uk (5)

Rhian Gabe; email: rhian.gabe@york.ac.uk (1)

Keith Harding; email: hardingkg@cf.ac.uk (6)

Alison Layton; email: alison.layton@hdft.nhs.uk (7)

Ellie Lindsay; email: ellie@legclubfoundation.com (8)

Catriona McDaid; email: catriona.mcdaid@york.ac.uk (1)

Christine Moffatt; email: christine.moffatt@nottingham.ac.uk (9)

Ceri Phillips; email: C.J.Phillips@swansea.ac.uk (10)

Gerard Stansby; email: Gerard.Stansby@nuth.nhs.uk (11)

Peter Vowden; email: peter.vowden@mac.com (12)

Laurie Williams; email: laurie.williams49@gmail.com

David Torgerson; email: david.torgerson@york.ac.uk (1)

Robert J Hinchliffe; email: rhinchli@sgul.ac.uk (2,3)

1) Department of Health Sciences, York Trials Unit, University of York, UK
2) St George's Vascular Institute, St George's Healthcare NHS Trust, UK
3) St George's University of London, UK
4) Hull York Medical School, University of Hull, UK
5) School of Nursing, Midwifery and Social Work, University of Manchester, UK
6) Wound Healing Research Unit, Cardiff University, UK
7) Harrogate and District NHS Foundation Trust, UK
8) The Lindsay Leg Club Foundation, UK
9) School of Health Sciences, University of Nottingham, UK
10) Swansea Centre for Health Economics, Swansea University, UK
11) School of Surgical & Reproductive Sciences, Newcastle University, UK
12) University of Bradford, UK

Corresponding Author:

Mr Robert J Hinchliffe

St George's Vascular Institute, St James' Wing, St George's Healthcare NHS Trust,

Blackshaw Road, London, UK, SW17 0QT. Email: rhinchli@sgul.ac.uk

Abstract

Background: Venous leg ulcers (VLUs) are the commonest cause of leg ulceration, affecting 1 in 100 adults. There is a significant health burden associated with VLUs – it is estimated that the cost of treatment for one ulcer is up to £1300 per year in the NHS. The mainstay of treatment is with graduated compression bandaging, however treatment is often prolonged and up to one quarter of venous leg ulcers do not heal despite standard care. Two previous trials have suggested that low-dose aspirin, as an adjunct to standard care, may hasten healing, but these trials were small and of poor quality. Aspirin is an inexpensive, widely used medication but its safety and efficacy in the treatment of VLUs remains to be established.

Methods / design: AVURT is a phase II randomised double blind, parallel-group, placebo-controlled efficacy trial. The primary objective is to examine whether aspirin, in addition to standard care, is effective in patients with chronic VLUs (i.e. over 6 weeks in duration or a history of VLU). Secondary objectives include feasibility and safety of aspirin in this population. A target of 100 participants, identified from community leg ulcer clinics and hospital clinics, will be randomised to receive either 300mg of aspirin once daily or placebo. All participants will receive standard care with compression therapy. The primary outcome will be time to healing of the reference ulcer. Follow-up will occur for a maximum of 27 weeks. The primary analysis will use a Cox proportional hazards model to compare time to healing using the principles of intention to treat. Secondary outcomes will include ulcer size, pain evaluation, compliance and adverse events.

Discussion: The AVURT trial will investigate the efficacy and safety of aspirin as a treatment for VLU and will inform on the feasibility of proceeding to a larger phase III study. This study will address the paucity of information currently available regarding aspirin therapy to treat VLU.

Trial registration: The study is registered on a public database with clinicaltrials.gov (NCT02333123; registered on 5th November 2014).

Key words: Leg ulcer, venous ulcer, wound healing, aspirin, compression therapy

Background

Venous leg ulcers (VLUs) are wounds of the lower limb caused by a diseased venous system, typically occurring in the gaiter area of the leg. VLUs represent the most common cause of leg ulceration, with a lifetime prevalence of 1-3% in UK adults and accounting for around 85% of all lower limb ulcers [1].

Many VLUs take over 6 months to heal; one large study demonstrated a median time to ulcer healing of 99 days with two-layer compression therapy [2]. In addition, more than a quarter fail to heal completely [3] and the 12-month recurrence rate of healed VLUs may be up to 28% [4 5]. Patients with longstanding, large ulcers, or who have a prior history of ulceration, are particularly resistant to healing [6 7]. VLUs impair quality of life; they are open wounds, which can be large, are often painful, frequently become infected and leak exudate. Compression bandaging is an effective treatment [8] but requires the use of sometimes bulky bandages alongside the need for regular clinic visits. Health-related quality of life (QoL) is decreased in patients with VLUs, which can incur significant psychological morbidity[9], and successful treatment has been

shown to significantly improve QoL [10]. VLUs represent a significant health economic burden, costing up to £1300 to treat one VLU episode for a year in the UK [11]. There is therefore an unmet need for a more cost-effective and clinically effective treatment for VLUs.

Pathophysiology of venous leg ulcers

In a healthy individual, flow of venous blood back to the heart occurs via the superficial venous system through the deep venous system, using the calf muscle pump and the venous valves to facilitate this flow against gravity. Resting hydrostatic venous pressure in the lower limb is 80mmHg in the standing position, with no pressure gradient. When exercising, pressure in the deep venous system exceeds 80mmHg, due to contraction of the calf muscles, forcing blood flow towards the heart. Valves in the superficial and perforator venous systems close to prevent retrograde flow. When the leg muscles relax again, pressure in the deep system falls below 80mmHg, allowing blood to flow from the superficial system to the deep system through patent valves. Any dysfunction along this pathway may contribute to the development of venous ulceration.

VLUs most commonly result from impaired venous return due to calf muscle pump failure, usually as a result of obstruction or valve dysfunction in the superficial, deep or perforator venous system in the leg (primary venous disease). VLU may also occur following a deep vein thrombosis or trauma (secondary venous disease). Other important factors include obesity and immobility.

Pathological maladaptation underlying VLU include structural changes in vessel walls such as intimal hyperplasia, increased collagen content in areas of hypertrophy, as well as reduced smooth muscle cells and extracellular matrix [12]. These changes are likely triggered by inflammation and contribute to loss of venous tone and, ultimately, venous reflux and hypertension. These structural changes are also accompanied by cellular changes in the wound and wound bed - increased proteolytic activity, platelet aggregation and infiltration of leucocytes into the dermis, causing dermal fibrosis and leading to cutaneous changes such as lipodermatosclerosis, haemosiderin deposition and ulceration.

Haemodynamic changes resulting from venous hypertension also affect the microcirculation, promoting interstitial oedema and capillary leakage. This combination of inflammatory activities may cause the VLU to heal slowly, or not at all. Targeting and reversing these pathophysiological pathways is the focus of adjunctive drug treatment.

Current treatment of venous leg ulcers

Careful and regular clinical assessment should be the first step in the management of venous ulceration and should ideally be performed in a specialised venous ulcer clinic. All patients should have a venous Duplex scan to assess for treatable venous disease. Ulcer area and characteristics should be monitored over time, as the changing nature of an ulcer (depth, area, base, ulcer edge) can indicate progression of disease or healing. Bacteriological swabs and antibiotics should only be used in cases of proven clinical infection and a biopsy may be considered in cases of atypical or non-healing ulceration. Simple dressings, meticulous wound care and judicious sharp debridement should be

undertaken by experienced practitioners. All patients with VLUs should have ankle brachial pressure index (ABPI) performed prior to the instigation of treatment to exclude arterial disease and should have cardiovascular risk factors addressed in the presence of an abnormal ABPI, in addition to referral to a vascular surgeon. Compression therapy should be instigated and undertaken by an appropriately trained professional. According to SIGN guidelines, patients with chronic non-healing VLU and concomitant superficial venous reflux should be referred for consideration of surgery to prevent recurrence [13].

Compression therapy

The standard treatment of VLUs is multi-layered compression bandaging (aiming for a pressure of 40mmHg at the ankle [14] with the aim to reduce venous hypertension, improve calf muscle function and create a wound environment that encourages healing whilst reducing tissue maceration and excessive oedema and moisture. Compression is recommended as first-line treatment for VLU in major UK guidelines [13].

The gold standard is 4-layer multi-component compression therapy [15], however this is often considered unsightly and uncomfortable, due to the bulky nature of the bandages, and may restrict movement at the ankle, making it difficult to wear shoes. In addition, poor application technique may reduce the effectiveness of compression and the negative physical and social impact of compression stockings may lead to ambivalence about their effectiveness and subsequent non-compliance[16]. 2-layer compression stockings are an alternative to 4-layer bandaging and a recent randomised trial has demonstrated a reduction in ulcer recurrence with the 2-layer approach[17] [2]. Various single-layer hosiery are also

available, however these do not meet the 40mmHg targeted compression pressure.

Topical therapy

Topical therapies have been used for VLUs (including silver-containing antibiotics, zinc oxide and other topical antimicrobials or impregnated dressings) although there is no reliable evidence to suggest that complex wound dressings are better than simple non-adherent dressings [18]. Topical local anaesthetic creams may help bring symptomatic relief when the ulcers are painful.

Adjunctive drug treatment

Various drug adjuncts to compression have also been investigated, with a recent Cochrane Review demonstrating that pentoxyfilline (a vasodilator that decreases blood viscosity, modifies leucocyte activity and has some anti-platelet effects) is effective in improving wound healing when used with, and possibly without, 4-layer compression [19]. However, vasodilators such as pentoxyfilline are not routinely prescribed in the NHS and may have intolerable adverse events, including potentially life-threatening side-effects such as haematemesis, gastrointestinal haemorrhage and thrombocytopenia [20]. There is insufficient evidence to recommend the use of other adjunctive drugs, including venoactive drugs that increase venous tone via mechanisms that remain largely unclear.

Aspirin

Aspirin is a cyclooxygenase inhibitor that irreversibly reduces prostaglandin-2 and thromboxane A2, which are involved in inflammation and platelet aggregation[21]. It is inexpensive, widely used and readily available. The mechanism by which aspirin may hasten healing of VLU is unclear but may be associated with a reduction of inflammation, or its effect on the microvascular circulation, including platelet activation. In one study investigating the haemostatic effects of aspirin in patients with VLU, the investigators demonstrated that participants were found to have increased levels of fibrinogen and shortened coagulation rate, when compared to age- and sex-matched controls and that treatment with aspirin caused prolongation of the coagulation rate, which increased the rate of ulcer healing [22].

There have been two small randomised trials to date that have investigated the use of aspirin (300mg) in VLUs, however the quality of evidence presented was low and more robust studies are required to confirm their findings. An additional file outlines the previous studies investigating aspirin in VLU [see Additional File 1].

The first study was carried out in 1994 and demonstrated that 38% more patients healed in the treatment group (aspirin plus compression) than in the control group (placebo plus compression)[23], however no patients healed within 4 months in the control group, which is surprising, given that the median time to healing with compression alone is around 3 months [15]. Although it provides some limited data about the potential use of aspirin therapy, the sample size of only 20 patients is insufficient to draw meaningful conclusions. In addition, patients were only followed up for 4 months.

Over a decade later, a Spanish group conducted a small randomised pilot trial (n=51 patients) of aspirin and compression, demonstrating that aspirin reduced the average time to healing but did not influence the rate of healing and had no effect on the rate of ulcer recurrence. In addition, after multivariate analysis was performed, aspirin was not demonstrated to be an independent predictor of healing [24] with only initial ulcer size at study entry remaining independently associated with rate of healing . Moreover, no information was presented regarding the placebo and there is uncertainty around the effect estimates. The quality of evidence that aspirin hastens healing of VLUs is therefore low and needs addressing through more robust studies.

In addition to the AVURT trial, there are two ongoing randomised trials investigating the use of aspirin in VLU. ASPiVLU (ASPirin in Venous Leg Ulcer healing, ACTRN12614000293662) will investigate the use of 300mg aspirin, in addition to standard 3-layer compression therapy, with the primary endpoint as the time to complete ulcer healing at or before 12 weeks from randomisation. Aspirin4VLU (Low Dose Aspirin for Venous Leg Ulceration, NCT02158806) will investigate 150mg aspirin, in addition to routine care, on time to complete healing of the reference ulcer. In addition to the trials reporting individually, data from AVURT, ASPiVLU and Aspirin4VLU will be combined in order to carry out an individual patient data (IPD) meta-analysis. Any other relevant trials such as the two earlier trials will also be considered for inclusion.

Other options: surgery and minimally invasive intervention

Varicose vein surgery for VLUs has not been shown to influence the time to VLU healing, however may decrease the rate and severity of recurrence [4, 25].

Minimally invasive techniques such as radiofrequency ablation, foam sclerotherapy and endovascular laser ablation have largely replaced traditional open surgical techniques in the treatment of varicose veins, where possible. There have been no large-scale randomised trials investigating the superiority of one technique over another when treating VLUs, although recent studies suggest some benefit from radiofrequency ablation to assist VLU healing [26]. However, a large multi-centre randomised trial is currently underway (EVRA – Early Venous Reflux Ablation ulcer trial), aiming to assess the influence of early endovenous treatment of superficial venous reflux in patients with VLUs, compared to standard compression therapy (NIHR HTA 11/129/197; ISRCTN02335796).

Other options: cell-based therapy, skin grafts and acellular products

Research on novel treatments with cell-based therapy is currently in progress, with promising results from phase II and phase III trials investigating the use of allogenic cells, either applied topically or via injection onto areas of ulceration [27] [28] as well as growth factors [29]. However such therapies are expensive, may be associated with significant side effects and are unlikely to become widely available in the near future. Accellular products, such as porcine mucosa, have been trialled to assist VLU healing, with promising results noted in one study [30]. A recent Cochrane Review of skin grafting for VLU (including autografts, allografts, xenografts and bioengineered artificial skin grafts) demonstrated that bilayer tissue-engineered skin replacement, used with compression, was the only skin grafting technique that may increase the rate of VLU healing [31], but data are very limited in this area.

The need for AVURT – a randomised, placebo-controlled efficacy study

Whilst there have been two small trials to date that have investigated the use of aspirin in the treatment of VLUs, the quality of the evidence presented is low. Given the significant health burden represented by VLUs, and the challenges in treating the disease, there is a need to identify effective, inexpensive, safe and widely available treatments that patients may tolerate. The Aspirin for Venous Ulcers: Randomised Trial (AVURT) seeks to investigate the effect of aspirin on time to healing of VLU, to examine safety issues in this cohort of patients and to inform on the feasibility of proceeding from a phase II trial to an efficacy and effectiveness (phase III) trial. If a simple, cheap and well tolerated medication, such as aspirin, were to result in a reduction in time to healing, this would impact on patient management, resource use and the potential impact on the population is substantial, given that aspirin is widely available. Meta-analyses have demonstrated that low-dose aspirin increases the risk of major bleeding compared to placebo [32, 33], however the absolute increase is modest and there is no evidence that decreasing the dose will reduce the risks of side effects [34]. The study will also provide the opportunity to systematically review the safety profile of aspirin in this population of patients, as well as assess the generalisability of the medication by studying the number of patients with VLUs who are currently taking aspirin or other anti-platelet medications.

Methods / design

Trial design

The AVURT trial is designed to inform the feasibility of a larger, confirmatory study of aspirin therapy for VLU. AVURT is a phase II randomised, double blind,

parallel-group, placebo-controlled study to provide evidence regarding the efficacy and safety of aspirin (at a dose of 300mg once daily), in addition to standard care in patients with chronic VLUs. A chronic VLU is defined as any break in the skin that has either: a) been present for more than six weeks, or b) occurred in a person with a history of venous leg ulceration. Ulcers will be considered venous if no other aetiology is clinically suspected. The ulcer must be venous in appearance (i.e. moist, shallow and irregular of appearance) and lie wholly or partially within the gaiter area of the leg. Potential participants will be identified from hospital outpatient clinics or community leg ulcer clinics, where they usually receive treatment for VLU. An additional file shows the schematic of the AVURT trial design [see Additional File 2]. All participants will continue to receive 'standard care' according to an evidence-based standardised approach to the management of VLU, as per SIGN guidelines [13] with multi-component compression therapy aiming to deliver 40mmHg at the ankle. The type of dressing used will be at the discretion of the healthcare professional managing the patient and will be documented in the participant case report form (CRF).

Aspirin will be provided as a 300mg capsule identical in weight, colour and size to the matched placebo capsules. Placebo capsules will contain a lactose and magnesium stearate blend. Capsules will be packaged into child-resistant tamper evident bottles sufficient in size to hold 190 doses for the participant to complete 24 weeks treatment.

Ethical approval

Full ethical approval has been granted by the NRES East Midlands – Nottingham 2 ethics committee (reference 14/EM/1305).

Screening, eligibility and patient pathway

Screening will be conducted by research nurses, who will also identify potential participants, gain informed consent and conduct a baseline assessment. Patients will be recruited from hospital and community based ulcer clinics, and through liaison with GPs, community nurses and hospital staff. Eligibility will be confirmed by a doctor. The participant will continue with regular (usually weekly or two-weekly) visits to the usual place of ulcer care, where the research or treating nurse will assess the components involved in the study. An additional file shows a summary of AVURT assessments [see Additional File 3].

Inclusion criteria

Inclusion criteria are:

- Patients with at least one chronic venous leg ulcer (if more than one ulcer, the largest ulcer will be chosen as the reference ulcer for the purposes of the trial)
- Ulcer area >1cm^2
- Ankle brachial pressure index (ABPI) ≥0.8 taken within the previous three months, *or*
- If the ABPI is incompressible, other forms of clinical assessment must exclude peripheral arterial disease (peripheral pulse examination, toe pressure, duplex ultrasound, clinical judgement)
- Age over 18 years (no upper age limit)

- Informed consent

Exclusion criteria

The exclusion criteria are:

- Unable to provide consent
- Unwilling to provide consent
- Foot ulcer (i.e. below the ankle)
- Leg ulcer of non-venous aetiology
- Ankle-brachial pressure index (ABPI) <0.8 or, where ABPI is not compressible, PAD cannot be excluded by other assessments
- Regular concomitant aspirin
- Previous intolerance or contraindication to aspirin use (according to prescriber's clinical judgement)
- Prohibited medication: probenecid; oral anticoagulants including coumarins (warfarin, acenocoumarol) and phenindione; dabigatran; rivaroxaban; apixiban; heparin; clopidogrel; dipyridamole; sulfinpyrazone and iloprost
- Known lactose intolerance
- Pregnant / lactating women
- Male or pre-menopausal female participants of child-bearing potential* unwilling to use an effective method of birth control (either hormonal in the form of the contraceptive pill or barrier method of birth control accompanied by the use of a proprietary spermicidal foam/gel or film ; or agreement of true abstinence (i.e. withdrawal, calendar, ovulation,

symptothermal and post ovulation are not acceptable methods) from time consent is signed until 6 weeks after the last dose of IMP

- Already participating in another study investigating leg ulcer therapy
- Previously been recruited into this trial
- Another reason that excludes them from participating within this trial (decision made according to the nurses' or prescribers' clinical judgment)

*Subjects are only considered not of child bearing potential if they are surgically sterile (i.e. they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal.

There will be no exceptions (waivers) to eligibility criteria. Participants will be considered eligible if they meet all of the inclusion criteria and none of the exclusion criteria mentioned above. Details of all screened patients, whether recruited or not, will be entered onto the sponsor screening log.

Consent

The process of consent will be carried out in accordance with the Declaration of Helsinki. All patients will be fully informed about the nature of the research study and the chances of being randomised to either the trial drug (aspirin) or placebo. Written information will be provided to patients, who will have the opportunity to discuss the study with a member of the trial team prior to enrolment in the study. Patients will be aware that their decision to participate in the study is voluntary and that they are free to withdraw consent at any time with no effect on the standard treatment they receive. Written consent forms

will be obtained from patients willing to participate in the study and will be retained by the investigator.

Randomisation and blinding

Participants will be randomised on a 1:1 basis to receive either aspirin (300mg) or placebo, in addition to standard care. The Research Pharmacy responsible for dispensing all trial medication (St George's Hospital) will receive a randomisation schedule generated in advance by the IMP manufacturer, Sharp Clinical Services UK Ltd. Stratification will be by ulcer size (≤5cm^2 or >5cm^2). Randomisation will be performed by the Research Pharmacy upon receipt of a valid prescription for a participant. Researchers, treating staff, clinicians and participants will be blind to treatment allocation. A 24-hour code breaking service will be provided by the Research Pharmacy in case of requirement for emergency unblinding and participants will receive a study-specific 24-hour emergency contact card.

Sample size calculation

This study aims to recruit 100 patients, which is sufficient to demonstrate whether there is evidence for efficacy of aspirin to treat VLUs, in line with previous similar trials [23,24]and is also large enough to test the feasibility of study procedures such as recruitment.

The primary outcome is time to healing of the reference ulcer. Applying an assumed standard error for the hazard ratio (HR) of 0.105 following adjustment for log area and log duration of ulcer (as in VenUS IV)[2] to the smaller sample size in this study implies that the standard error would be 0.22. A 95% confidence

interval for the log hazard ratio would thus be log(HR) ± 0.435. Hence if the hazard ratio for this study were the same as that suggested by previous studies (around 1.5), the confidence interval would be (0.97, 2.31) which just includes 1.00. To further increase the power an IPD meta-analysis is proposed. As compliance and follow-up will be measured as part of the study there is no formal inflation for dropout.

An important secondary outcome is wound area. Assuming a standard deviation of 1.09 following log transformation as in (VenUS I)[15], two groups of 50 participants will render 80% power to detect a difference of 0.62 on the natural log scale. This corresponds to a reduction of 46% in ulcer area at follow-up. In the current study, there will be multiple measurements of wound area and so smaller differences should be detectable.

Primary outcome

The primary outcome is time to ulcer healing, which will be defined as 'completed epithelial healing in the absence of scab (eschar) with no dressing required'. This will take the form of survival time data for analysis. Time to healing will be measured in days from the date of randomisation until the first date that healing is recorded. If healing occurs before the end of the study, the participant will be followed for a further two weeks to confirm healing, in accordance with the FDA and EWMA guidelines [35]. A digital photograph of the area will be taken at this point to confirm healing. For patients who have not healed, time from date of randomisation until they exit the trial, withdraw, are lost to follow up or die will be used in the survival analysis – whichever occurs first.

Secondary outcomes

Secondary outcomes are:

- Ulcer size (area) measured in cm^2 using image analysis by SigmaScan, Systat Software Inc, California and / or wound tracings
- Recurrence of reference ulcer
- Adverse events
- Ulcer-related pain using a visual analogue scale
- Treatment compliance (capsule counting and nurse assessment of compression concordance)
- Resource use: number of wound consultations and types of dressings used

Statistical analysis

Analyses will be in accordance with the principles of intention to treat. Analysis will be conducted in Stata ® (Stata Corporation, College Station, Texas, USA) or similar statistical software. Statistical significance will be assessed at the two-sided 5% level unless otherwise stated. 95% confidence intervals will be provided as appropriate. Statistical analyses will be detailed in an analysis plan that will be independently reviewed and agreed before data are analysed.

<u>Primary outcome analyses</u>

Time to ulcer healing will be presented by trial arm using a Kaplan-Meier plot and a log-rank survival comparison will be made. The median time to healing will be presented overall and by trial arm with corresponding 95% CIs. The

primary analysis will investigate differences between trial arms in relation to time to ulcer healing using a Cox proportional hazards regression model. Adjustments will be made for log transformed area and duration of the reference ulcer. The model will be tested for inclusion of shared centre frailty effects.

Secondary outcome analyses

Ulcer area will be transformed and investigated on the natural log scale through mixed models to see whether there are differences by trial arm.

The proportion of patients who are found to have a recurrence within the study period will be reported by trial arm. Time from healing to recurrence will be investigated in a similar fashion to the primary outcome should numbers be sufficient to allow.

Adverse events will be reported overall and by trial arm in terms of number of patients with at least one event and total number of events. Serious and non-serious events will be presented separately and according to whether they are thought to be related, or unrelated, to treatment. Differences in total numbers of events by trial arm will be compared using negative binomial regression adjusting for size and duration of ulcer.

Mean and median pain scores will be presented by trial arm and differences in pain scores between the allocated groups will be investigated using linear regression adjusted for baseline pain score.

Compliance will be reported in terms of proportion of patients completing the course of treatment up to healing or planned trial exit and compared between arms using a Chi-squared test and 95% confidence intervals.

Resource use will be presented using summary statistics in relation to the number of wound consultations per week and change to compression therapy or primary wound dressings.

Treatment period and follow-up

After consent, participants will be screened to ensure eligibility. Prior to randomisation, baseline demographic details will be collected and a clinical assessment of the patient and wound performed. Following randomisation, participants will continue in the normal care pathway of weekly or two-weekly clinical assessments at community ulcer clinics, hospital outpatient clinics or home visits and will not be required to attend any further visits for research purposes. All randomised participants will receive aspirin or placebo for 24 weeks and will be followed up for 25 weeks following randomisation. If the reference ulcer is confirmed as healed during the follow-up period, then a photograph will be taken and the participant will continue to take the IMP or placebo for 2 further weeks. They will then be re-assessed (as per FDA and EWMA guidelines on wound healing)[35]. If the ulcer is confirmed as healed at this reassessment visit, then the date of ulcer healing will be recorded as the date that the ulcer was first assessed as healed. The participant will then be advised to stop taking the IMP or placebo. If a new ulcer occurs on the reference leg before the end of the study, then participants will be asked to inform the study team.

If the ulcer is assessed as 'not healed', then the participant will continue in the trial until the minimum period of follow up (25 weeks) has elapsed providing confirmed healing does not occur before the end of the follow up period. Both of

these time-points (first healing judgement and confirmation of ulcer healing) will be recorded.

Participants will also be asked to provide a pain score using a visual analogue scale at baseline and 4-6 weeks after first dose of IMP. Weekly (or two-weekly, if that is the participant's usual interval of care) assessments will include: healing outcomes, treatment concordance with IMP and compression bandaging, adverse events or side effects, change to concomitant medication, resource use (number of visits, types of dressings used and level of compression). Digital photographs, or leg ulcer tracings, will also be taken by the treating or research nurse.

Safety reporting

Despite some apparent advantages of aspirin therapy in the treatment of VLUs, the risks associated with aspirin will carefully reported. Safety reporting during this trial is paramount and will be conducted in line with HTA guidelines. Reportable safety events will include any of the following experienced by a participant during the trial: adverse event, adverse reaction, serious adverse event, serious adverse reaction, suspected unexpected serious adverse reaction. All adverse events (AEs) will be recorded in the clinic notes, on the study case report form and reported to the sponsor via the sponsor AE log. Serious adverse events (SAEs) and serious adverse reactions (SARs) will be notified to the sponsor immediately when the investigator becomes aware of the event (within 24 hours). The sponsor will inform the MHRA and ethics committee, where appropriate. SAEs will be reported to the trial coordinator in the York Trials Unit via the sponsor and reviewed by the data monitoring committee.

All patients who develop unacceptable treatment toxicity which, in the investigator's opinion, is attributable to the IMP or an SAE will be withdrawn from the study treatment but follow-up will continue (where appropriate) to enable an intention to treat analysis. The side effects associated with aspirin are well known to health professionals and no additional training will be required. These include, but are not limited to, gastrointestinal haemorrhage and gastrointestinal disturbance (including dyspepsia, ulceration).

In addition, adverse events associated with leg ulceration or compression therapy will be recorded. Pregnancy and breastfeeding are exclusion criteria for the study, however all patients of childbearing age will be advised to use barrier contraception during the duration of the study.

Discussion / Summary

Chronic VLUs are a common medical problem associated with considerable morbidity. Current treatment (using graduated compression therapy) may not result in sustained wound healing, however there is inadequate evidence of other effective alternatives, or adjuncts, to improve outcomes. Low-dose aspirin (in addition to standard compression therapy) may hasten healing, however current evidence supporting its use is insufficient. This randomised trial will inform on whether low-dose aspirin is an effective, feasible and safe therapy for patients with chronic VLUs, in addition to standard compression therapy. This could go some way towards addressing the significant health burden associated with VLUs.

Trial status

At the time of submission, the trial is open to recruitment. Collaborating centres include St George's, University of London; University of York; University of Manchester; Bradford Teaching Hospitals NHS Foundation Trust; Harrogate & District NHS Foundation Trust; Hull and East Yorkshire Hospitals NHS Trust; University of Nottingham; Cardiff University; Newcastle University.

List of abbreviations

VLU: venous leg ulcer; QoL: quality of life; ABPI: ankle brachial pressure index; HTA: Health Technology Assessment; NHS: National Health Service; SIGN: Scottish Intercollegiate Guidelines Network; MHRA: Medicines and Healthcare products Regulatory Agency; REC: research ethics committee; IMP: investigational medicinal product; FDA: Food and Drug Administration; EWMA: European Wound Management Association.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RH is the Chief Investigator, conceived the study and has led on all stages of the study design and protocol development. RF wrote the manuscript with RH and is involved in image analysis and data collection. DT, CMcD, HT, DR, LCl, LCo, JD, CM, EL, IC, KH, GS, and CP helped with study design, protocol development and edited the manuscript. MB, RG, HB provided statistical expertise, study design,

protocol development and edited the manuscript. PV, AL, LW helped with study design and protocol development. All authors approved the final manuscript.

Authors' information

RH is reader and honorary consultant in vascular surgery at St George's Vascular Institute, University of London, UK. RF is a vascular specialist registrar on the London training programme, UK. DR is a regulatory assurance manager at St George's University of London, UK. DT is professor and director of York Trials Unit, UK. CMcD is a senior research fellow in the Department of Health Sciences; HT is a research fellow and trial manager in the Department of Health Sciences; MB is professor of health statistics; RG is senior statistician; HB is statistician; LCl is a trial coordinator; LCo is a research fellow – all at the University of York, UK. JD is senior lecturer in applied health research at the University of Manchester, UK. CM is professor of clinical nursing at the University of Nottingham, UK. EL is founder and president of the Leg Club Foundation, UK. IC is professor of surgery at Hull York Medical School, UK. KH is professor and head of wound healing at Cardiff University, UK. GS is professor and consultant vascular surgeon at Newcastle University, UK. CP is professor of health economics and head of the college of human and health sciences at Swansea University, UK. PV is professor and consultant vascular surgeon at Bradford Teaching Hospitals NHS Foundation Trust and the University of Bradford, UK. AL is consultant dermatologist at Harrogate and District NHS Foundation Trust. LW is a lay representative.

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Additional file 1

AVURT table 1.doc. Previous randomised trials investigating aspirin in the treatment of VLU.

Additional file 2

AVURT schematic.pdf. Schematic of AVURT trial design.

Additional file 3

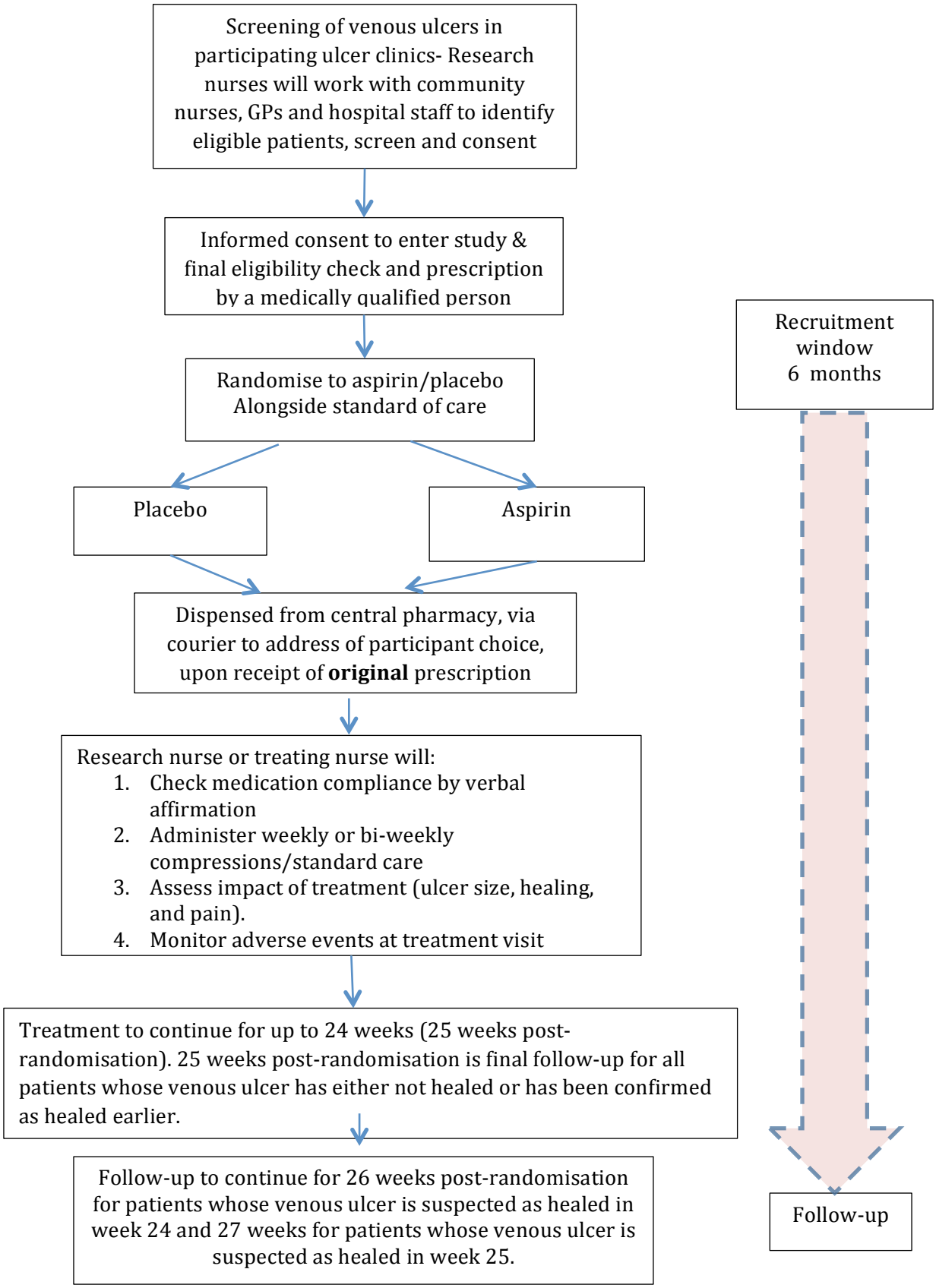
AVURT figure 2.pdf. Summary flow chart of AVURT assessments.

Table 1: Previous randomised trials investigating aspirin in the treatment of VLU

Author	**Year**	***n***	**Type of study**	**Treatment group**	**Control group**	**Main results**
Layton	1994	20	Double-blind randomised	Aspirin 300mg plus compression	Placebo plus compression	Ulcer healing within 4 months: 38% in treatment group vs 0% in control group (p<0.007). Reduction in ulcer size: 52% in treatment group vs 26% in placebo group (p<0.007).
del Río Solá	2012	51	Double-blind randomised	Aspirin 300mg plus compression	Compression only	Complete healing: no difference between groups. Time to healing: 12 weeks in treatment group vs 22 weeks in control group (p=0.04). Ulcer recurrence: no difference between groups. Initial area of injury was the only variable that influenced the rate of healing.

Additional File 2

Click here to download Figure AVURT schematic.pdf



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