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Abstract

AVURT: aspirin versus placebo for the treatment of venous leg ulcers – a Phase II pilot randomised controlled trial

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Background: Venous leg ulcers (VLUs) are the most common cause of leg ulceration, affecting 1 in 100 adults. VLUs may take many months to heal (25% fail to heal). Estimated prevalence is between 1% and 3% of the elderly population. Compression is the mainstay of treatment and few additional therapies exist to improve healing. Two previous trials have indicated that low-dose aspirin, as an adjunct to standard care, may improve healing time, but these trials were insufficiently robust. Aspirin is an inexpensive, widely used medication but its safety and efficacy in the treatment of VLUs remains to be established.

Objectives: Primary objective – to assess the effects of 300 mg of aspirin (daily) versus placebo on the time to healing of the reference VLU. Secondary objectives – to assess the feasibility of leading into a larger pragmatic Phase III trial and the safety of aspirin in this population.

Design: A multicentred, pilot, Phase II randomised double-blind, parallel-group, placebo-controlled efficacy trial.

Setting: Community leg ulcer clinics or services, hospital outpatient clinics, leg ulcer clinics, tissue viability clinics and wound clinics in England, Wales and Scotland.

Participants: Patients aged ≥ 18 years with a chronic VLU (i.e. the VLU is > 6 weeks in duration or the patient has a history of VLU) and who are not regularly taking aspirin.

Interventions: 300 mg of daily oral aspirin versus placebo. All patients were offered care in accordance with Scottish Intercollegiate Guidelines Network (SIGN) guidance with multicomponent compression therapy aiming to deliver 40 mmHg at the ankle when possible.

Randomisation: Participants were allocated in a 1 : 1 (aspirin : placebo) ratio by the Research Pharmacy, St George's University Hospitals NHS Foundation Trust, using a randomisation schedule generated in advance by the investigational medicinal product manufacturer. Randomisation was stratified according to ulcer size (≤ 5cm^2 or > 5cm^2).

Main outcome measure: The primary outcome was time to healing of the largest eligible ulcer (reference ulcer).

Feasibility results – recruitment: 27 patients were recruited from eight sites over a period of 8 months. The target of 100 patients was not achieved and two sites did not recruit. Barriers to recruitment included a short recruitment window and a large proportion of participants failing to meet the eligibility criteria.

Results: The average age of the 27 randomised participants (placebo, $n = 13$; aspirin, $n = 14$) was 62 years (standard deviation 13 years), and two-thirds were male ($n = 18$). Participants had their reference ulcer for a median of 15 months, and the median size of ulcer was 17.1 cm^2. There was no evidence of a difference in time to healing of the reference ulcer between groups in an adjusted analysis for log-ulcer area and duration (hazard ratio 0.58, 95% confidence interval 0.18 to 1.85; $p = 0.357$). One expected, related serious adverse event was recorded for a participant in the aspirin group.

Limitations: The trial under-recruited because many patients did not meet the eligibility criteria.

Conclusions: There was no evidence that aspirin was efficacious in hastening the healing of chronic VLUs. It can be concluded that a larger Phase III (effectiveness) trial would not be feasible.

Trial registration: Clinical Trials.gov NCT02333123; European Clinical Trials Database (EudraCT) 2014-003979-39.

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List of abbreviations

ABPI	ankle–brachial pressure index
ACCEPT	Acceptance Checklist for Clinical Effectiveness Pilot Trials
AE	adverse event
AR	adverse reaction
AVURT	Aspirin for Venous leg Ulcers Randomised Trial
BMI	body mass index
BS-21	21-point Box Scale
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
GP	general practitioner
HR	hazard ratio
HTA	Health Technology Assessment
ID	identifier
IMP	investigational medicinal product
IQR	interquartile range
MHRA	Medicines and Healthcare products Regulatory Agency
NIHR	National Institute for Health Research
PAD	peripheral arterial disease
PIC	patient identification centre
R&D	research and development
RCT	randomised controlled trial
REC	Research Ethics Committee
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	visual analogue scale
VenUS IV	Venous leg Ulcer Study IV
VLU	venous leg ulcer
YTU	York Trials Unit

Plain English summary

We conducted a small randomised controlled trial to look at whether or not a daily dose of 300 mg of aspirin may help to heal venous leg ulcers. The aim of the trial was also to enable a decision to be made about whether or not a large trial should be undertaken to confirm our results. We also looked at whether or not aspirin is safe to use in people with leg ulcers. We aimed to recruit 100 patients from leg ulcer clinics. Half of the patients recruited received 300-mg capsules of aspirin and the other half received a dummy drug (placebo). Both groups also received the usual ulcer treatment of compression therapy and dressings. Participants and doctors were unaware whether an individual had received aspirin or the dummy drug.

We measured how long it took the largest ulcer to heal as the main measure of treatment success. We also measured changes in the size of participants' reference (largest eligible) ulcer over 6 months using photographs and tracings of the wound outline, and collected information about the amount of pain caused by the ulcer, how often participants took the study drug and the number of visits participants had to the hospital or their general practitioner.

We concluded that a larger trial recruiting the same type of patients would not be possible as we recruited only 27 participants instead of the 100 participants that we were aiming for. The main reasons that we could not recruit more patients in the time available were that many patients were already taking aspirin and/or their ulcer was smaller than the ulcer size we were investigating. Aspirin appears to be safe in this population; however, because we only recruited a small number of participants, we were unable to confirm if it might be effective for healing leg ulcers.

Scientific summary

Background

Venous leg ulcers (VLUs) are wounds of the lower limb caused by disease of the venous system that result in chronically swollen legs and damage to the tissues, usually around the ankles. Chronic ulcers are those present for ≥ 6 weeks or those that are recurrent. VLUs may take many months to heal and 25% fail to heal. Estimated prevalence of VLUs is between 1% and 3% of the elderly population. At present, compression is the mainstay of treatment for VLU and few additional therapies exist to improve healing. This has been shown to be effective in many clinical trials. However, despite this treatment, patients take many months to heal (with median healing times of approximately 12 weeks in previous trials) and, for some patients, compression therapy does not result in resolution of their leg ulcers.

Objectives

The objectives were to assess the efficacy of aspirin for time to healing of chronic VLUs, to examine the safety of this aspirin intervention in this cohort of patients and to inform the feasibility of study procedures, such as recruitment, in order to proceed from a Phase II trial to a Phase III randomised controlled trial of clinical effectiveness and cost-effectiveness.

Primary objective

To compare the effects of 300 mg of aspirin plus standard care with placebo plus standard care on time to healing of the reference chronic VLU (largest eligible venous ulcer).

Secondary objectives

To assess the safety of aspirin in patients with VLUs and feasibility of leading directly from the pilot Phase II trial into a larger pragmatic study (Phase III) of effectiveness and efficiency, and check, in accordance with the Acceptance Checklist for Clinical Effectiveness Pilot Trials (ACCEPT) criteria, whether or not the pilot study fulfilled four criteria:

1. confirming that the effect sizes in the British and Spanish RCTs were too large, but
2. confirming that smaller effect sizes were still plausible, while
3. confirming that the intervention does not lead to unacceptably high rates of serious adverse events (SAEs), and
4. confirming that we can recruit at the planned rate.

Design

The Aspirin for Venous leg Ulcers Randomised Trial (AVURT) was a multicentred, pilot, Phase II randomised double blind, parallel-group, placebo-controlled efficacy trial. Participants were randomised to receive 300 mg of aspirin or placebo in a 1 : 1 ratio.

Setting

Participants were recruited from 10 centres in England, Wales and Scotland that were treating leg ulcers. Centres were recruited throughout the trial.

Participants

Inclusion criteria

To be eligible for the study, it was necessary for participants to meet all of the following criteria.

- Having at least one chronic VLU, that is, the VLU has (1) been present for > 6 weeks or (2) occurred in a person with a history of venous leg ulceration. Ulcers were considered purely venous if clinically no other aetiology was suspected. The ulcer was required to be venous in appearance (i.e. moist, shallow, of an irregular shape) and lie wholly or partially within the gaiter region of the leg. If the patient had more than one ulcer, then we chose the largest ulcer as the reference ulcer for purposes of the analysis.
- Having an ulcer with an area of > 1 cm^2.
- Having had an ankle–brachial pressure index (ABPI) of ≥ 0.8 taken within the previous 3 months or, when the ABPI is incompressible, other accepted forms of assessment included peripheral pulse examination/toe pressure/Duplex ultrasonography in combination with clinical judgement to be used to exclude peripheral arterial disease.
- Being aged ≥ 18 years (there was no upper age limit).
- Being able to provide informed consent.

Exclusion criteria

Potential participants were excluded if they fulfilled any of the following criteria.

- Being unable or unwilling to provide consent.
- Having a foot (below the ankle) ulcer.
- Having a leg ulcer of non-venous aetiology (i.e. arterial).
- Having an ABPI of < 0.8.
- Using (self-administered or prescribed) regular concomitant aspirin.
- Having a previous intolerance of aspirin/contraindication to aspirin (decision made according to the prescribers' clinical judgement).
- Taking contraindicated medication: probenecid, oral anticoagulants including coumarins [warfarin and acenocoumarol (Sinthrome®, Merus Labs Luxco S.a.R.L., Amsterdam, the Netherlands)] and phenindione (Dindevan®, Concordia International Corp., Oakville, ON, Canada), dabigatran (Pradaxa®, Boehringer Ingelheim Limited, Bracknell, UK), rivaroxaban (Xarelto®, Bayer AG, Leverkusen, Germany), apixiban (Eliquis®, Bristol-Myers Squibb, New York, NY, USA), heparin, clopidogrel, dipyridamole, sulfinpyrazone and iloprost.
- Having known lactose intolerance.
- Being a pregnant or lactating/breastfeeding woman.
- Being male or a pre-menopausal female of child-bearing potential unwilling to use an effective method of birth control.
- Currently participating in another study evaluating leg ulcer therapies.
- Having another reason that excluded them from participating within this trial (decision made according to the nurses' or prescribers' clinical judgement).
- Having previously been recruited to this trial.

Patients were pre-screened on the basis of three criteria (concomitant aspirin, wound size and ulcer duration or history of venous ulceration) by study research nurses to determine which patients might be eligible for the study.

Interventions

A 300-mg dose of daily oral aspirin for 24 weeks (four × 75-mg tablets were encapsulated in size 00 capsules with added lactose and magnesium stearate blend as filler) and placebo (size 00 capsules with lactose and magnesium stearate blend as filler, which were identical in weight, colour and size to the aspirin capsules).

All participants were offered an evidence-based standardised approach to the management of their leg ulcers in accordance with Scottish Intercollegiate Guidelines Network (SIGN) guidance. This consisted of multicomponent compression therapy aiming to deliver 40 mmHg of pressure at the ankle, when possible. The type of dressing used was at the discretion of the health-care professionals managing the participants.

Randomisation

Recruiting sites contacted the Research Pharmacy (St George's University Hospitals NHS Foundation Trust, London, UK), which conducted the random allocation. Patients were randomly allocated in a 1 : 1 ratio to either aspirin or placebo using a randomisation schedule generated by the investigational medicinal product (IMP) manufacturer in advance. Randomisation was stratified according to ulcer size (≤ 5 cm^2 or > 5 cm^2), as ulcer size is the strongest predictor of outcome. The randomisation identifier on the schedule corresponded to IMP bottle number.

Participants, investigators, research and treating nurses and other attending clinicians were blind to treatment throughout the trial. There was a 24-hour emergency code break facility at the Research Pharmacy.

Outcome measures

Outcome measures included time to healing of the reference ulcer (primary outcome), ulcer size, adverse events (AEs), ulcer recurrence (following healing), ulcer-related pain measured using a visual analogue scale (VAS), treatment compliance and resource use.

Methods

Outcome assessments were made by research nurses or treating nurses weekly or fortnightly for a minimum of 25 weeks post randomisation.

Following the confirmation of a participant's eligibility, and before randomisation, a baseline assessment was conducted by the study or research nurse, including participant details and ulcer history assessment. Digital photographs and tracings were taken, as was information on baseline ulcer-related pain.

Measurement of primary outcome

Healing was defined as complete epithelial cover in the absence of a scab (eschar) with no dressing required. This was determined by the treating nurse or research nurse and a digital photograph was taken of the wound area. After the ulcer was initially judged to be healed, participants were followed for a further 2 weeks to confirm healing.

Measurement of secondary outcomes

The reference ulcer was measured using wound grid tracings at screening, baseline and at final follow-up and at other follow-up visits when a photograph could not be taken.

Ulcer-related pain was collected at baseline and at weeks 4, 5 and 6 after randomisation using a 21-point box scale.

Participant concordance with treatment (IMP and compression) was recorded in the weekly case report forms (CRFs) and at the end of the study with return of the empty container to the Research Pharmacy, which undertook a pill count.

Resource use was recorded on CRFs, with change to type of changes of dressing/compression recorded as well as the number of wound consultations.

At each follow-up appointment, treating nurses asked participants if they had experienced any SAEs, AEs or adverse reactions and indicated the participant's response ('yes' or 'no') in the CRFs.

Participants were deemed to have exited the trial when they withdrew consent, were lost to follow-up, died or had completed follow-up.

Results

The original participant recruitment window was extended from 6 to 8 months owing to poor patient recruitment.

The main reasons for participant ineligibility were:

- already taking aspirin or other prohibited medication
- having a small or otherwise ineligible ulcer.

Modifying the eligibility criteria to improve recruitment was not possible except for adopting a smaller wound size. However, this was rejected as ulcers with a wound area of < 1 cm^2 usually heal very rapidly.

There were external factors outside the control of the research team that meant that sites were slow to open. A range of options were considered and explored to improve recruitment, including recruitment from primary care. Preliminary searches of records in primary care also indicated very few potentially eligible participants. In addition, the trial's short recruitment window and budget constraints meant that many of the options considered were not viable without a funded extension.

Analyses were conducted following the principles of intention to treat with all events analysed according to the participant's original treatment allocation. Pre-screening was under-reported as the first pre-screening log was not completed by some sites. The number of patients for whom we had pre-screening data was 457 and the number of participants who consented was 29. Two patients were excluded after consent was given and before randomisation.

The average age of the 27 randomised participants was 62 years [standard deviation (SD) 13 years], and two-thirds were male ($n = 18$). Participants had had their reference ulcer for a median of 15 months and the median size of ulcer was 17.1 cm^2.

There was one withdrawal during the course of the study (placebo), for whom data on primary outcome were not possible to obtain. This was reported at week 2 and so no follow-up data are available for this patient beyond week 1. The other four patients (placebo, $n = 2$; aspirin, $n = 2$) either agreed to withdraw from treatment but provided full follow-up until week 25 or healed at a point before withdrawal and, thus, all four provided primary outcome data.

Overall, 13 out of the 26 participants (50.0%) who were followed up were recorded as healing during the course of the study. All the reference ulcers reported to be healed on a CRF were confirmed healed approximately 2 weeks later. Seven out of 12 participants (58.3%) followed up in the placebo group and 6 out of 14 (42.9%) in the aspirin group were observed to have a healed reference ulcer. It was not possible

to estimate median time to healing and/or corresponding 95% confidence intervals (CIs) because less than, or close to, half of the patients were observed to have healed during the follow-up period of the study.

The primary analysis investigated the difference in time to healing by trial arm. Hazard ratios (HRs) and corresponding 95% CIs were obtained from a Cox regression model adjusted for ulcer area and ulcer duration at baseline (both logarithmically transformed): the HR of aspirin versus placebo (allocation) was 0.58 (95% CI 0.18 to 1.85; $p = 0.36$). Overall, these data do not provide evidence of a difference in time to healing with the addition of aspirin to usual care. The numbers within this feasibility study are small and results are inconclusive in terms of the primary outcome.

Secondary outcomes

Adverse events

Six out of the 26 (23.1%) participants who were followed up had no reported AEs (placebo, $n = 3$; aspirin, $n = 3$) and the remaining 20 had AEs (placebo, $n = 9$; aspirin, $n = 11$). The total number of events experienced by participants was compared by trial arm, adjusting for the prognostic factors (log of baseline reference ulcer area and log of baseline reference ulcer duration) using negative binomial regression as per the statistical analysis plan. There was no evidence that participants receiving aspirin were more likely to suffer an AE than those receiving placebo (incidence rate ratio 1.31, 95% CI 0.51 to 3.41; $p = 0.58$).

One participant suffered one SAE during the course of the study, requiring a blood transfusion for gastrointestinal bleeding. There were 88 non-serious AEs (placebo, $n = 36$; aspirin, $n = 52$) recorded in total among 20 participants (placebo, $n = 9$; aspirin, $n = 11$). The majority of these were not related to the IMP.

The mean baseline VAS score for ulcer-related pain was 37.7 (95% CI 22.0 to 53.4) in the placebo group and 45.4 (95% CI 24.6 to 66.2) in the aspirin group; the mean VAS score at week 5 was 13.3 (95% CI 0.3 to 26.3) in the placebo group and 28.5 (95% CI 10.6 to 46.3) in the aspirin group.

Of the 13 participants who healed, 12 were assessed for ulcer recurrence using the recurrence assessment form. Recurrence was reported for two patients (placebo, $n = 1$; aspirin, $n = 1$).

Participants took their first dose of study drug a median of 4 days after randomisation (range 1–12 days) and the majority took their first dose in the morning (70.8%; placebo, $n = 9$; aspirin, $n = 8$).

Compliance

The mean number of visits attended up until healing or study exit was 13.3 (SD 7.3) and 17.4 (SD 6.8) in the placebo and aspirin groups, respectively. Ten out of the 12 participants (83.3%) in the placebo group and 10 out of the 14 participants (71.4%) in the aspirin group were fully compliant with their compression therapy. Two participants in the placebo group (16.7%) and four participants in the aspirin group (23.1%) were partially compliant.

Eight out of the 12 participants (66.7%) in the placebo group were deemed fully compliant with taking the study medication while four (33.3%) were partially compliant. In the aspirin group, 11 out of the 14 participants (78.6%) were deemed fully compliant and three (21.4%) were partially compliant.

All participants in the placebo group were prescribed high-level compression therapy (≥ 40 mmHg) at baseline and, of those in the aspirin group, 12 were prescribed high-level compression therapy and two medium-level compression therapy (20–39 mmHg).

The total number of changes to the compression therapy prescribed at baseline during the study was 16, with five changes (31.3%) to a medium-compression level, nine changes (56.3%) to a high-compression level, one change (6.2%) to a low-compression level and one change (6.2%) to no compression at all.

The mean number of wound consultations per week was 2.1 (SD 1.4) in the placebo group, 1.9 (SD 0.7) in the aspirin group and 2.0 (SD 1.0) overall.

One participant was unblinded after the trial had completed and analysis was being undertaken, in accordance with the emergency unblinding procedure. There were no protocol violations.

Conclusions

AVURT was a Phase II randomised pilot trial of aspirin versus placebo for the treatment of patients with chronic venous leg ulceration. It was not possible to recruit the planned number of patients despite an unfunded extension to the trial and, therefore, it can be concluded that a larger Phase III (effectiveness) trial would not be feasible.

Trial registration

This trial is registered as Clinical Trials.gov NCT02333123 and European Clinical Trials Database (EudraCT) 2014-003979-39.

Funding

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

Chapter 1 Background

Chronic venous leg ulcers

Chronic venous leg ulcers (VLUs) are wounds of the lower limb caused by a diseased venous system, which results in swollen legs and damage to the tissues, usually around the ankles. VLUs are most commonly the result of severe varicose veins, a previous deep-vein thrombosis, trauma or failure of the calf muscle pump, all of which result in impaired venous return. Obesity and immobility are additional important factors contributing to venous dysfunction.[1]

The VLUs may take many months to heal (with approximately 25% failing to heal completely), during which time they result in significant suffering and reduction in quality of life for patients.[2] VLUs have a tendency to become recurrent, with rates of recurrence estimated at between 18% and 28%.[3] As a result, the management of VLUs represents a substantial cost to the NHS, the majority of which is attributed to nurse time. Estimated lifetime prevalence of VLUs is between 1% and 3% of the elderly population in the USA and Europe.[4] It is estimated that 1% of the adult population will suffer from leg ulcers at some point in their life.[5] Furthermore, incidence and prevalence of ulceration is predicted to increase as a result of the increasing age and obesity of the population in the USA and Europe. A recent cohort study conducted in the UK estimated that 278,000 VLUs per year are managed by the NHS.[6] Furthermore, the annual cost to the NHS of this management was estimated to be £941M, with substantially more cost associated with unhealed wounds.[7]

Current treatment strategies

Current treatment strategies for VLUs focus on efforts to reduce venous hypertension. At present, compression is the main treatment for venous ulceration and few additional therapies have robust evidence to suggest they improve healing rates.

Compression therapy

The mainstay of treatment of leg ulcers is graded compression therapy (target pressure of 40 mmHg) and this is the recommended first-line treatment in UK guidelines.[2] The aim of compression therapy is the reduction of venous hypertension, improvement in calf muscle function and the creation of a wound environment conducive to wound healing. Compression therapy in the form of bandages and hosiery has been shown to be effective in many randomised controlled trials (RCTs).[8] However, despite this treatment, patients take many months to heal (with median healing times of approximately 12 weeks in previous trials)[3] and for some patients compression therapy does not result in resolution of their leg ulcers. The use of compression (as well as dressings, largely to manage the wound exudate) can be expensive as nurse time is required to change bandages, which can be required weekly or more frequently.

In addition, effective treatment of VLU requires adherence to compression therapy which, for many patients, is uncomfortable and sometimes painful and inconvenient for everyday life (compression is bulky and dressings have to be changed several times weekly). In addition, the use of thicker bandaging systems, such as four-layer bandaging, may restrict movement of the ankle and cause difficulty in wearing shoes.[9]

Topical therapies

The most frequently used topical antimicrobials in wound care practice are chlorhexidine, iodine, silver-containing products, mupriocin (Bactroban®, GlaxoSmithKline, Brentford, UK) and fucidic acid. Historically, agents such as acetic acid, honey, hydrogen peroxide, sodium hypochlorite, potassium permanganate and proflavine have all been used.[10] There is currently a lack of reliable evidence to support an association between topical agents and reduction in time to healing in VLUs.[11]

Adjunctive drug therapies

A recent Cochrane review has shown pentoxifylline to be an effective adjunct to compression therapy and possibly more effective than placebo or no treatment in the absence of compression.[12] However, pentoxifylline is not commonly prescribed in the NHS[13] and has common and intolerable side effects, some of which have the potential to be life-threatening.[14] Other adjunctive drugs, including venoactive drugs, are not recommended owing to insufficient evidence regarding their use and unclear mechanism of action.[15]

Surgery

Surgery to treat superficial varicose veins has been shown to prevent recurrence of ulcers once they have healed but does not improve time to healing of existing ulcers.[16] An ongoing RCT is further investigating surgery as a treatment for chronic ulceration, comparing early versus delayed endovenous treatment of superficial venous reflux.[17] This study is due to publish in November 2018.[17]

Other therapies

Research into the use of novel cell-based therapies, such as allogenic cells and growth factors, is currently in progress.[18–20] Owing to their cost and associated side effects, it is thought that such therapies are unlikely to be made widely available.[18] If other treatments were able to reduce the time to healing, this would be a significant breakthrough.

Potential role of aspirin as a treatment for venous leg ulcers

Aspirin (also known as acetylsalicylic acid) has been widely used as a medication for > 100 years and is inexpensive, readily available and generally safe to use. Aspirin is a cyclo-oxygenase inhibitor that irreversibly reduces prostaglandin 2 and thromboxane A2.[21] At low doses, it is used very widely to reduce cardiovascular events in those at high risk.[22]

The exact mechanism by which aspirin may improve time to healing of VLUs is unclear but it is potentially associated with both the inhibition of platelet activation and the reduction of inflammation.[23]

Possible adverse events (AEs) associated with the use of aspirin include gastric ulceration and other gastrointestinal effects. Other effects include liver and renal toxicity, exacerbation of asthma and dermatological reactions. Antiplatelet drugs, when administered in combination with anticoagulants, are associated with a higher risk of gastrointestinal bleeding than that associated with each drug class used alone.[24]

Existing evidence on aspirin in the treatment of venous leg ulcers

To date, there have been two small RCTs that have investigated the use of aspirin (300 mg/day) in patients with VLUs of ≥ 2 cm^2 in area. The first, a UK-based study in 20 participants, reported healing of 38% of ulcers in the intervention group (aspirin in combination with compression therapy), compared with 0% in the control group (placebo in combination with compression therapy), over a study period of 4 months. The average time to healing was not reported.[25] del Río Solá *et al.*[26] reported a study of 51 participants to whom aspirin was given in combination with compression therapy ($n = 23$) compared with compression therapy alone ($n = 28$). The researchers reported the average time to healing as 12 weeks in the aspirin group compared with 22 weeks in the control group, but that there was no significant difference between groups in the proportion of patients with ulcers healed (74% in the aspirin group and 75% in the control group). These two studies were the only RCTs identified in a recently conducted Cochrane systematic review[23] and, owing to variations and limitations in the data, a meta-analysis was not undertaken. Application of GRADE (Grading of Recommendations, Assessment, Development and Evaluations)[27] to the data highlighted that the evidence was of low to very low quality.

Explanation of rationale

The Aspirin for Venous leg Ulcers Randomised Trial (AVURT) was undertaken to address the primary question of whether or not the addition of 300 mg of daily aspirin to standard evidence-based therapies demonstrates evidence of a reduction in time to healing of VLUs. This pilot trial was developed to explore this question as well as assessing the feasibility (especially in terms of participant recruitment and treatment compliance) and safety (in terms of aspirin-related AEs) of conducting a larger-scale pragmatic study, powered to investigate the clinical effectiveness and cost-effectiveness of aspirin for VLU healing.

This research is important because leg ulcers are common and costly and result in significant patient suffering.[2] If aspirin, which is commonly used in many patients, was able to reduce the time to healing of VLU with limited risk of treatment-related harm, then this would result in a potentially important reduction in resource use and an improvement in patients' health-related quality of life. Because aspirin is generally safe, cheap, well tolerated (for most patients) and widely available, the potential impact on this population is large.

Two previously conducted RCTs have been performed on the use of aspirin in the treatment of VLUs.[25,26] The findings of both trials suggested that there may be benefit in patients with VLUs taking aspirin: one reported that a greater proportion of patients healed with 300 mg of aspirin together with standard compression bandaging[25] and one reported a shorter time to healing with 300 mg of aspirin in conjunction with gradual compression therapy.[26] However, both trials have been assessed as being at a risk of bias.[23] The authors of the Cochrane review[23] concluded that the low-quality and insufficient evidence from the two included trials meant that they were unable to make definitive claims on the benefits and potential harm of oral aspirin, as an adjunct to compression therapy, on the recurrence and healing of VLUs. The Cochrane review[23] recommended that further high-quality studies were needed.

A RCT is required to assess the potential effectiveness and safety profile of aspirin in this population. However, it would be premature to conduct a full trial initially, not least as it is not clear how many people with VLUs currently take aspirin or other antiplatelet medications and the potential impact of this on the design and feasibility of any future study.

During the registration of AVURT, we identified two other RCTs investigating aspirin for VLUs. ASPiVLU (ASPirin in Venous Leg Ulcer Healing)[28] was a trial being conducted in Australia that was planning to randomise patients with VLU to receive either 300 mg of aspirin or placebo. The primary end point of that study was time to complete healing of reference ulcer at or before 12 weeks post randomisation. Aspirin4VLU (Low Dose Aspirin for Venous Leg Ulcers) was a trial being conducted in New Zealand that was planning to randomise VLU patients to either 150 mg of aspirin or placebo in addition to standard care. The primary end point was time to complete healing of reference/largest ulcer. A secondary outcome of this study is change in estimated reference ulcer area from baseline to 24 weeks.[29]

Research objectives

To assess the efficacy of aspirin on time to healing of VLUs, to examine safety issues in this cohort of patients and to assess the feasibility of proceeding from a Phase II trial to a Phase III trial of clinical effectiveness and cost-effectiveness.

Primary objective

To compare the effects of 300 mg of aspirin plus standard care with placebo plus standard care on time to healing of the reference chronic VLU (largest eligible venous ulcer).

Secondary objectives

To assess the safety of aspirin in patients with VLUs and feasibility of leading directly from the pilot Phase II trial into a larger pragmatic study (Phase III) of effectiveness and efficiency, and check, in accordance with the Acceptance Checklist for Clinical Effectiveness Pilot Trials (ACCEPT) criteria,[30] whether or not the pilot study fulfilled four criteria:

1. confirming that the effect sizes in the British and Spanish RCTs were too large, but
2. confirming that smaller effect sizes were still plausible, while
3. confirming that the intervention does not lead to unacceptably high rates of serious adverse events (SAEs), and
4. confirming that we can recruit at the planned rate.

Additional objective

To perform an individual patient-level meta-analysis using the data from AVURT and other published[25,26,31] and unpublished studies [e.g. A Carolina Weller Barker, I Darby, T Haines, M Underwood, S Ward, P Aldons, E Dapiran, JJ Madan, P Loveland, A Sinha, M Vicaretti, R Wolfe, M Woodward, J McNeiJ (ASPiVLU). School of Public Health and Preventative Medicine, Monash University, Melbourne, VIC, Australia, 2015]. The objective of performing this meta-analysis is to assess the clinical effectiveness on time to healing of VLUs and safety of aspirin use. This will take place following completion of the other trials, which are still recruiting patients[28,29] at the time of writing.

Chapter 2 Methods

This chapter reports the methods used to conduct AVURT. It describes the study design and protocol from recruitment of participants to completion in the study, data analysis procedures, quality assurance and governance. The trial protocol has been published.[32]

Design

A multicentred, pilot, Phase II randomised double-blind, parallel-group, placebo-controlled efficacy trial.

Setting

Patients presenting at community leg ulcer clinics/hospital outpatients' clinics, or registered with a leg ulcer clinic but receiving care at home, were recruited. Some sites could use patient identification centres (PICs) to identify patients to take part. Participants were recruited from 10 centres in England, Wales and Scotland (see *Appendix 1*) from leg ulcer hospital outpatient clinics ($n = 5$), community leg ulcer clinics or community caseloads ($n = 3$), a wounds clinic in a university ($n = 1$) and a primary care leg ulcer clinic ($n = 1$). At each of the nurse-led community centres ($n = 3$), a doctor was identified to work with the centre to review and confirm the patient's eligibility for the trial, to prescribe the investigational medicinal product (IMP) and to review changes to concomitant medication.

Participants

Participant eligibility for the trial was assessed according to the criteria below.

Inclusion criteria

To be eligible for the study, it was necessary for participants to meet all of the following criteria.

- Having at least one chronic VLU, when chronic venous leg ulceration was defined as any break in the skin that had either (1) been present for > 6 weeks or (2) occurred in a person with a history of venous leg ulceration. Ulcers were considered purely venous if clinically no other aetiology was suspected. The ulcer was required to be venous in appearance (i.e. moist, shallow, of an irregular shape) and lie wholly or partially within the gaiter region of the leg. If the patient had more than one ulcer we chose the largest as the 'index' or reference ulcer for purposes of the analysis.
- Having an ulcer with an area of > 1 cm^2.
- Having had an ankle–brachial pressure index (ABPI) of ≥ 0.8 taken within the previous 3 months or, when the ABPI is incompressible, other accepted forms of assessment included peripheral pulse examination/toe pressure/Duplex ultrasonography in combination with clinical judgement to be used to exclude peripheral arterial disease (PAD).
- Being aged ≥ 18 years (there was no upper age limit).
- Being able and willing to give informed consent.

Exclusion criteria

Potential participants were excluded if they fulfilled any of the following criteria.

- Being unable or unwilling to provide consent.
- Having a foot (below the ankle) ulcer.
- Having a leg ulcer of non-venous aetiology (i.e. arterial).
- Having an ABPI of < 0.8.

- Using (self-administered or prescribed) regular concomitant aspirin.
- Having a previous intolerance of aspirin/contraindication to aspirin (decision made according to the prescribers' clinical judgement).
- Taking contraindicated medication: probenecid, oral anticoagulants including coumarins (warfarin and acenocoumarol) and phenindione, dabigatran, rivaroxaban, apixiban, heparin, clopidogrel, dipyridamole, sulfinpyrazone and iloprost.
- Having known lactose intolerance.
- Being a pregnant or lactating/breastfeeding woman.
- Being male or a pre-menopausal female of child-bearing potential unwilling to use an effective method of birth control [i.e. either hormonal in the form of the contraceptive pill; barrier method of birth control accompanied by the use of a proprietary spermicidal foam/gel or film; or agreement of true abstinence (withdrawal, calendar, ovulation, symptothermal and post ovulation were not acceptable methods)] from the time consent was signed until 6 weeks after the last dose of IMP. Participants were only considered not of child-bearing potential if they were surgically sterile (i.e. they had undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they were postmenopausal.
- Currently participating in another study evaluating leg ulcer therapies.
- Having another reason that excluded them from participating within this trial (decision made according to the nurses' or prescribers' clinical judgement).
- Having previously been recruited to this trial.

Recruitment

Patients were pre-screened on the basis of three criteria (concomitant aspirin, wound size and ulcer duration or history of venous ulceration) by study research nurses to determine those potentially eligible for the study. The reason(s) for ineligibility or not approaching patients were recorded on pre-screening logs (see *Appendix 2*). Two pre-screening logs were issued. Completion of the first log (version 1.0) was non-mandatory as stipulated by the trial sponsor (based on the sponsor's belief that the clinics received a heterogeneous referral pattern of mixed aetiology ulcers not thought to be truly representative of the total population of patients with chronic VLUs). Following a recommendation by the Data Monitoring Committee (DMC), the sponsor permitted a new pre-screening log that was made mandatory (version 2.0). Patients attending clinics as part of their routine care and who satisfied the pre-screening criteria were approached by study research nurses or designated health-care professionals and provided with both verbal and written information about the trial in a face-to-face meeting (see *Appendix 3*). Patients were given a minimum of 24 hours to consider participation in the trial. Study research nurses then obtained voluntary full written consent from those patients who wanted to enter the trial (see *Appendix 4*). After they gave consent, patients were screened against the study's full eligibility criteria by the study research nurses or designated health-care professionals using the screening case report form (CRF) (see *Appendix 5*). The reason(s) for a patient's ineligibility were recorded. Patients were informed that their eligibility would be subject to confirmation by a medical practitioner and in all cases a medical practitioner determined and confirmed patient eligibility following screening. If a potential participant was not known to the medical practitioner, provision was made for the participant to be contacted by telephone by the medic to check for any possible contraindications. When the medic was satisfied of patient eligibility, they would sign off the prescription for the IMP (see *Appendix 6*).

Randomisation

Patients were randomly allocated in a 1 : 1 ratio to either aspirin or placebo by the Research Pharmacy (St George's University Hospitals NHS Foundation Trust, London, UK). Randomisation was stratified according to ulcer size (≤ 5 cm^2 or > 5 cm^2) as this is the strongest known predictor of outcome.[4]

Sequence generation

The aspirin and placebo manufacturer, Sharp Clinical Services (UK) Limited (registered office in Ashby-de-la-zouch, UK), generated the randomisation schedule in advance. They provided one randomisation list to the Research Pharmacy and a copy to the senior trial statistician in the York Trials Unit (YTU; University of York). To facilitate participant allocation according to stratification, the allocation sequence on the randomisation list was mirrored top to bottom bottom to top, and each allocation was referenced 1 to 120 for participant identifier (ID). Where the participant was placed on the randomisation list (top or bottom) depended on the stratification of ulcer size (≤ 5 cm^2 or > 5 cm^2).

Allocation

After participant consent was taken and baseline data were recorded, the research site faxed the AVURT prescription directly to the Research Pharmacy. The AVURT prescription also indicated ulcer size.
On receipt of the original signed prescription by post, the Research Pharmacy allocated the next available randomisation ID. The randomisation ID corresponded to IMP bottle number for allocation (top or bottom), in accordance with the ulcer size stratification as indicated on the prescription. IMP was dispensed by St George's and sent by courier under temperature-controlled conditions directly to all participants. The date of randomisation, a unique patient ID and a unique screening ID were recorded by the Research Pharmacy on a Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) spreadsheet, which was sent to the YTU each week or when a participant was randomised.

Blinding

Participants, investigators, research and treating nurses and other attending clinicians were unaware of the trial drug allocation throughout the trial. There was a 24-hour emergency code break facility at the Research Pharmacy for health professionals to contact if they needed to determine whether or not patients were receiving aspirin or placebo for onward clinical management. However, in practical terms, it was expected that most clinicians would treat participants with AEs on the assumption that they had been randomised to receive aspirin.

Interventions

Intervention group

Intervention: 300 mg of daily oral aspirin for 24 weeks (four × 75-mg tablets were encapsulated in size 00 capsules with added lactose and magnesium stearate blend as filler).

Control group

Placebo: daily oral placebo for 24 weeks. Size 00 capsules with lactose and magnesium stearate blend as filler, which were identical in weight, colour and size to the aspirin capsules.

The full course of capsules (190 doses/capsules for 24 weeks' treatment) were packaged into child-resistant tamper-evident bottles. Participants were advised to take the capsules whole (not crushed or chewed), once a day for 24 weeks or, if the reference ulcer was confirmed as healed before the end of 24 weeks, a member of the medical team would advise them to stop taking the medication. The time of day for taking the trial medication was not specified.

Participants were expected to receive and start their allocated trial treatment from 2 to 7 days after randomisation.

All participants were offered an evidence-based standardised approach to the management of their leg ulcers in accordance with Scottish Intercollegiate Guidelines Network (SIGN) guidance.[33] This consisted of multicomponent compression therapy aiming to deliver 40 mmHg of pressure at the ankle, when possible. The type of dressing used was at the discretion of the health-care professionals managing the participants.

Investigational medicinal product supply

The sponsor had responsibility for the order and purchase of trial medication and for arranging labelling of medication for the trial with St George's University Hospitals NHS Foundation Trust.

Manufacture, packaging and labelling

Active (aspirin) tablets were manufactured by Intrapharm Laboratories Limited, Maidenhead, UK. Overencapsulation of the 75-mg tablets and production of the matching placebo capsules was performed by Sharp Clinical Services (UK) Limited (MA IMP licence number 10284). Sharp Clinical Services (UK) Limited performed all manufacturing and packaging operations in accordance with good manufacturing practices derived from the rules governing Medicinal Products in the European Community and Good Manufacturing Practice for Medicinal Products.[34–36]

The AVURT IMP was assigned an expiry date of 31 May 2016. Following the extension to participant recruitment, the sponsor arranged for stability testing of the IMP with Sharp Clinical Services (UK) Limited. The testing was conducted and the expiry date was extended to 31 January 2017.

The supplies of aspirin and placebo capsules were delivered to the Research Pharmacy, where they were stored and dispatched to all participants.

Outcomes

Primary outcome

Time to healing of the reference ulcer (the largest eligible ulcer).

Secondary outcomes

- Ulcer size (area) measured in cm^2 by specialist software and grid tracings.
- Following healing of the reference ulcer, recurrence of ulcer on the reference leg (defined as a new ulcer on the reference leg).
- Adverse events.
- Ulcer-related pain using a visual analogue scale (VAS).
- Treatment compliance (capsule count and nurse assessment of compression concordance).
- Resource use: number of visits to clinic and/or home visits and types of dressings used.

Baseline assessment

Following confirmation of a participant's eligibility, and before randomisation, a baseline assessment was conducted by the study or research nurse using the baseline CRF (see *Appendix 7*).

Participant details

Data on ethnicity were collected at baseline. Participants' date of birth, gender and smoking status were collected at screening. Participants' contact details (name, address, telephone numbers and e-mail address) and general practitioner (GP) details (name of GP, name of surgery and address) were recorded at the recruiting site only.

Ulcer history and assessment

The last ABPI measurement of the reference leg (leg with the largest eligible ulcer) and date it was taken were recorded, or it was noted that the ABPI was unable to be taken. When ABPI was incompressible, other assessments to exclude PAD were permitted, including peripheral pulse examination/toe pressure/Duplex ultrasonography in combination with clinical judgement, but these forms of assessments were not recorded on the CRF.

Other items recorded were number of ulcers on the reference leg, approximate duration of reference ulcer (years, months and weeks), how long ago since patient developed their first leg ulcer (years, months and weeks), and total number of ulcer episodes on reference leg (leg with largest eligible ulcer) including the reference ulcer (largest eligible ulcer). All ulcers on both legs were drawn onto a leg diagram and the reference ulcer indicated.

Digital photographs and tracings

To measure ulcer area, a photograph and tracing of the reference ulcer were taken at baseline. Photographs were taken with a Nikon Coolpix L3 (Nikon Corporation, Tokyo, Japan), in accordance with trial procedure (see *Appendix 8*). Anonymised digital photographs were sent to the YTU using a secure electronic method. Sites unable to use this method were able to send anonymised photographs on a memory card via a courier service to the YTU or a collection could be made by one of the trial co-ordinators.

Tracings were taken using a fine-nibbed marker pen on a wound measurement grid composed of 1-cm^2 squares (P12v2, ConvaTec, Uxbridge, Middlesex, UK). The wound area was calculated by the treating or research nurse by totalling the number of squares and/or partial squares on the grid contained within the traced ulcer area.

Participant mobility, anthropometry and diabetic status

The level of a participant's mobility (walking and ankle mobility), their height (feet/inches or centimetres) and weight (stones/pounds or kilograms) were recorded. If both metric and imperial measurements were given, a check was conducted by the YTU to determine if they were equivalent. Any differences were queried with the site. Body mass index [BMI (kg/m^2)] was calculated using the formula: weight (kg) divided by height squared (m^2). The presence of type of diabetes mellitus (type 1 or 2) was recorded.

Current treatments received

Participants' medications at baseline were recorded by the study research nurse in a medication diary (see *Appendix 9*). The medication diaries were then given to participants for recording changes to non-trial medication. The participants were asked to bring their diary along to each clinic assessment for review by the study research nurse and site medical practitioner to check that participants were safe to continue with the IMP. Medication data were not collected for analysis.

Participants' current treatment(s) for their VLU were recorded (type of compression bandaging), as was the level of ankle pressure compression being aimed for (mmHg) and the primary dressing in contact with the ulcer.

Ulcer-related pain

Participants were asked to rate the intensity of any leg ulcer-related pain over the previous 24 hours using the 21-point Box Scale (BS-21).[37] The BS-21 is a VAS that is divided into units of five and ranges from a value of 0 (no pain) to 100 (worst pain imaginable).

Resource use

The treating or research nurse recorded resource use on the CRFs. They initially recorded the type of dressing administered and level of compression aimed for and subsequently, during follow-up, only recorded a change in the type of dressing administered and/or level of compression.

Outcome assessments

Participants were followed up weekly or fortnightly, depending on their usual pattern of attendance at clinic, for a minimum of 25 weeks post randomisation. Participants were not asked to make any additional visits for the purposes of the trial. The participant weekly data collection file, made up of CRFs and forms, was completed during follow-ups by research nurses or treating nurses (see *Appendix 10*). In addition,

recorded in the file were the weeks in which participants missed or did not have an appointment, the randomisation date, the date that the first IMP dose was taken and the time of day that the IMP was generally taken. A summary flow chart of participant follow-up is shown at *Appendix 11*.

Planned participant follow-up was for 25 weeks post randomisation, but participants who had a wound initially judged as healed in week 24 or 25 were followed up for 2 further weeks (26 and 27 weeks post randomisation, respectively) to confirm healing. *Table 1* summarises the schedule of assessments. All anonymised completed CRFs were faxed or sent via the University of York's secure electronic system to the YTU.

Measurement and verification of primary outcome measure

Time to healing of the reference ulcer

The treating or research nurse identified and monitored the reference ulcer. Healing was defined as complete epithelial cover in the absence of a scab (eschar) with no dressing required. Healing was determined by the treating nurse or research nurse and a digital photograph was taken of the wound area. Healing was reported by the treating site on Form D (see *Appendix 10*) which was submitted to the YTU. Time to healing was measured in days from the date of randomisation to the date that the ulcer was first assessed as healed. After the treating or research nurse initially judged the ulcer to be healed, participants were followed up for a further 2 weeks, in accordance with the Food and Drug Administration guidelines,[38] to confirm healing.

Measurement of secondary outcomes

Ulcer size

The reference ulcer was measured using wound grid tracings at screening, baseline and at final follow-up and at other follow-up visits when a photograph could not be taken. Treating nurses calculated the ulcer size by totalling the number of squares and/or partial squares on the grid contained within the traced ulcer area size and reported the measurement in the CRFs.

Anonymised digital photographs were taken at baseline and at all weekly or fortnightly follow-up visits. All digital images were checked and the ulcer size calculated using SigmaScan® software (Sigma Scan Pro version 5.0, SigmaScan, Systat Software Inc., San Jose, CA, USA) by one researcher, Rachael Forsythe (Specialist Registrar in Vascular Surgery, St George's Hospital, London, UK) who was blinded to treatment allocation.

Ulcer recurrence

Weekly follow-up CRFs were not completed for participants after their reference ulcer had been confirmed as healed. To collect ulcer recurrence data, participants were given a card with contact details for their recruiting site (see *Appendix 12*) and were asked to phone the clinic if they developed a new ulcer on their reference leg. In addition, at week 25 post randomisation, the research nurse phoned participants whose reference ulcer had healed, to collect data on leg ulcer recurrence. The date of recurrence of a new venous ulcer on the reference leg was recorded (see *Appendix 10*, *Form E*).

Ulcer pain

Participants were asked to rate the intensity of any leg ulcer-related pain over the previous 24 hours using the BS-21. Ulcer-related pain was collected at baseline and at weeks 4, 5 and 6 after randomisation. It was thought that aspirin might have a positive effect on pain. We required one pain score at follow-up but took measurements at three follow-up time points to allow for participants not being seen every week.

TABLE 1 Schedule of assessments

Study procedures	Screening	Baseline	During treatment (weekly for 25 weeks post randomisation)					Post treatment (only participants whose reference leg ulcer was judged as healed in weeks 24 and 25)	Post treatment (only participants whose reference leg ulcer was judged as healed in week 25)
			Week 1	Weeks 2–3	Weeks 4–6	Weeks 7–24	Week 25	Week 26	Week 27
Informed consent	✓								
Inclusion/exclusion criteria	✓	✓							
Demographics		✓							
Dispensing of IMP			✓						
Medical history	✓	✓							
Concomitant medication	✓	✓	✓	✓	✓	✓	✓[a]	✓	✓
AEs/side effects/change to health status			✓	✓	✓	✓	✓	✓	✓
Ulcer photograph[b]		✓	✓	✓	✓	✓	✓[a]	✓	✓
Tracing of ulcer	✓	✓					✓[a]		
Resource use: change to type of usual care/compression bandage administered			✓	✓	✓	✓	✓[a]	✓	✓
Compliance			✓	✓	✓	✓	✓[a]		
Pain score		✓			✓				
Ulcer reccurrence (only patients whose leg ulcer was confirmed as healed before week 25)							✓		

a Data was not collected from patients whose reference leg ulcer healed earlier in the trial.
b If a digital photograph of the ulcer could not be taken, then a tracing of the ulcer was made instead.

Participant compliance with treatment

To monitor treatment concordance with the IMP and compression, the treating nurses recorded in the weekly CRFs (see *Appendix 10*) how often a participant was taking the capsules and, when applicable, reasons for not taking them every day. Treating nurses also recorded whether or not a participant had fully, had partially, or had not complied with compression therapy, with reason(s) for non-compliance captured when possible.

At the end of the study, the remaining IMP or, in cases when participants had taken all the trial medication, the empty container, was returned to the Research Pharmacy, which undertook a pill count. This information was then forwarded to the YTU for inclusion in the analysis.

Resource use

At follow-up visits (weekly or fortnightly depending on a participant's usual pattern of care), changes to the level of compression therapy were recorded (see *Appendix 10*, *Form A*) and changes to the type of primary dressing or bandaging (see *Appendix 10*, *Form B*). The number of times participants had other wound consultations in the previous week was also recorded.

Patient safety

Each participant was regularly reviewed by their treating nurse and/or physician working closely with the AVURT research team and was continually assessed for any increased dyspepsia, other gastrointestinal symptoms, skin rashes and any other possibly linked AEs that could be attributable to the IMP.

Known side effects

Common side effects of aspirin as listed on the summary of product characteristics, which was supplied by the IMP manufacturer (Intrapharm Laboratories Limited), included increased bleeding tendencies and dyspepsia.

Adverse events: definitions

The following definitions were applied in the study.

Adverse event

- Any untoward medical occurrence in a patient or clinical trial participant who is administered an IMP and which does not necessarily have a causal relationship with this treatment, and which may include an exacerbation of a pre-existing illness.
- Increase in frequency or severity of pre-existing episodic condition.
- A condition (regardless of whether or not it was present prior to the start of the trial) that is detected after trial drug administration (this does not include pre-existing conditions recorded as such at baseline, continuous persistent disease or a symptom present at baseline).

Adverse reaction

- Any untoward and unintended responses to an IMP related to any dose administered.

Serious adverse event or serious adverse reaction

- Any AE or reaction that, at any dose, results in death.
- Any AE or reaction that, at any dose, is life-threatening (places the subject, in the view of the investigator, at immediate risk of death).

- Any AE or reaction that, at any dose, requires hospitalisation or prolongation of existing hospitalisation [hospitalisation is defined as an inpatient admission, regardless of length of stay, even if it is a precautionary measure for observation (including hospitalisation for an elective procedure and for a pre-existing condition)].
- Any AE or reaction that, at any dose, results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions).
- Any AE or reaction that, at any dose, results in a congenital anomaly or birth defect (in offspring of subjects or their parents taking the IMP regardless of time of diagnosis).
- Any AE or reaction that is related to another important medical condition.

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the outcomes listed in *Serious adverse event or serious adverse reaction* was also considered serious.

Suspected unexpected serious adverse reaction

A suspected unexpected serious adverse reaction (SUSAR) is an adverse reaction (AR) that is classed in nature as both serious and unexpected.

An unexpected AR is when both the nature and the severity of the event are not consistent with the reference safety information (RSI) available for the IMP in question.

Assessments

At each follow-up appointment, the treating nurses asked participants if they had experienced any changes in their health and indicated their response in the CRFs. Participants whose reference leg ulcer had healed, and, therefore, were no longer receiving follow-up appointments, were contacted at week 25 post randomisation by a research nurse who collected information on AEs that the participant had experienced since the last data collection point (see *Appendix 10*, *Form E*).

Details of the AEs/ARs were recorded in clinic notes and on AE logs held at the recruiting sites. The causality, severity and expectedness assessment was conducted by medically qualified doctors at the sites who were blind to treatment allocation in accordance with the following descriptions.

Causality assessment

- Definitely: there is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- Probably: there is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- Possibly: there is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (i.e. the patient's clinical condition, other concomitant events).
- Unlikely: there is little evidence to suggest that there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, or other concomitant treatments).
- Unrelated: there is no evidence of any causal relationship.
- Not assessable: note – if this description was used, then the sponsor assumed that the event was related to the IMP until follow-up information was received from the investigator to confirm a definitive causality assessment.

Any SUSAR assessed as related to the IMP was required to be reported to the sponsor, irrespective of how long after IMP administration the reaction had occurred.

Expectedness assessment

Assessment was based solely on the available RSI for the IMP and was described using following categories.

- Expected: an AE that is classed in nature as serious and that is consistent with the information about the IMP listed in the RSI or clearly defined in the study protocol.
- Unexpected: an AE that is classed in nature as serious and that is not consistent with the information about the IMP listed in the RSI.

All assessments were reviewed by the chief investigator using specific guidance notes from the National Institute for Health Research (NIHR) clinical trials tool kit.[39]

Reporting

Non-serious and serious AEs were reported by the sites to the trial manager at the YTU on the sponsor's AE log. SAEs were recorded on the sponsor's SAE form and reported directly to the sponsor (St George's University Hospital) within 24 hours of the local investigators becoming aware. The sponsor followed up SAEs to their resolution and was responsible for reporting the events to Research Ethics Committee (REC), the Medicines and Healthcare products Regulatory Agency (MHRA) and the trial manager at the YTU.

All AEs, ARs, SAEs and serious ARs were reviewed by the sponsor and chief investigator and subsequently the DMC (blinded to allocation), which made the final decision regarding the severity and causality and relationship between the event and treatment.

Withdrawal

Participants were deemed to have exited the trial when they:

- withdrew consent
- were lost to follow-up
- died
- had completed follow-up (i.e. 25 weeks post randomisation or, for patients whose leg ulcer was first assessed as healed in weeks 24 and 25, weeks 26 and 27, respectively).

If a participant chose to withdraw from the trial then reasonable effort was made to establish the reason for this withdrawal. For participants leaving the trial before final follow-up, nurses completed a change to study status form (see *Appendix 10*, *Form F*), giving the main reason for the participant's exit. No further follow-up data were collected. Participants withdrawing from the study were given the option for their data not to be used.

Participants stopped treatment for any one of the following reasons, but continued with follow-up:

- Unacceptable treatment toxicity that, in the investigator's opinion, is attributable to the IMP or a SAE.
- Intercurrent illness that prevents further protocol treatment.
- Any change in a participant's condition that, in the investigator's opinion, justified the discontinuation of treatment.
- If a participant became pregnant or suspected that they were pregnant.
- Reference ulcer confirmed as healed.
- A participant chose to discontinue treatment.

Participants whose leg ulcer was initially assessed as healed were encouraged to take the IMP during the 2-week observation period. If healing was confirmed after 2 weeks, the participant stopped taking the trial medication and follow-up was suspended until a final follow-up in week 25.

Sample size

The target sample size was 100 participants. This sample size is sufficient to test the feasibility of study procedures, such as recruitment and retention, and is large enough to demonstrate whether or not there is evidence for efficacy in line with two previous trials of aspirin for leg ulcers.[25,26]

The primary outcome was time to healing of the largest eligible leg ulcer (reference ulcer). Ulcer area and duration of ulcer are known prognostic factors for healing. In a previous leg ulcer study, Venous leg Ulcer Study IV (VenUS IV), after adjustment for log-area of ulcer and log-duration of ulcer, the standard error for the time to healing estimate was 0.105, with data on 448 participants.[3] Applying this to a smaller sample of 100 participants implies that the standard error of such a sample would be increased to 0.22 [obtained from $0.105 \times \sqrt{(448/100)}$]. A 95% confidence interval (CI) for the log-hazard ratio (HR) would thus be the estimate of the log (HR) $\pm$ $1.96 \times 0.222 = \log(\text{HR}) \pm 0.435$. The antilog of this is 1.54 and the 95% CI for the HR would be the observed value divided or multiplied by this. Hence, if our HR were the same as that suggested by the existing studies (i.e. about 1.5), then our CI would be 0.97 to 2.31, which just includes 1.00. It would be unlikely that, if the HR is as these two previous smaller studies suggest, we would observe an overall HR of < 1.00. Compliance and follow-up were measured as part of the study and so there is no formal inflation of the recruitment target for drop out.

A secondary outcome was change in wound area. Using data from the Venous leg Ulcer Study I (VenUS I) of compression bandaging,[40] ulcer area was measured for 245 participants who were measured within 60 days of recruitment. Ulcer area has a highly skewed distribution, so we calculated a difference in log-area at follow-up, after adjustment for log-ulcer area at baseline and time elapsed until follow-up. The residual standard deviation (SD) was 1.09. Two groups of 50 participants would give us 80% power to detect a difference of 0.62 on the natural-log scale, corresponding to a reduction of 46% in ulcer area at follow-up. In the current study, we had multiple measurements of wound area and so predicted that we should be able to detect smaller differences.

Statistical methods

The statistical methods for the analysis of the trial data were prespecified and detailed in a statistical analysis plan (SAP) before the completion of data collection. The SAP was prepared by the trial statisticians and reviewed by members of the Trial Management Group (TMG) and DMC. However, given that the final number of participants randomised was much lower than the 100 planned ($n = 27$), many of the pre-planned analyses were infeasible or inappropriate. In this section, we describe the analyses as performed, highlighting any deviations from the SAP.

Pre-screening, screening and eligibility data

The flow of participants through the trial is presented in a Consolidated Standards of Reporting Trials (CONSORT) diagram.[41] The number of patients who were pre-screened, were approached and consented is reported. Reasons for ineligibility at the pre-screening phase and reasons for not consenting are summarised.

Baseline data

Participant characteristics and clinical baseline measurements are summarised descriptively overall and by trial arm. These measures include age, gender, BMI, diagnosis of diabetes mellitus, ethnicity, participant's level of mobility and ankle mobility, reference ulcer size and corresponding stratification (≤ 5 cm^2 or > 5 cm^2), time since first ulcer, duration of reference ulcer (actually referring to the duration of the ulcer up to but not beyond randomisation), left/right reference leg, total ulcers on reference leg, ABPI of the reference ulcer, levels of pain from the reference ulcer, current compression and dressing treatments. Continuous measures were summarised using mean, SD, median, minimum, maximum and interquartile range (IQR). Categorical measures were reported as counts and percentages. No formal statistical comparisons of baseline factors by trial arm were undertaken.

Primary outcome

The primary analysis investigated the difference in time to healing by trial arm using Cox's proportional hazards regression adjusted for ulcer area (cm^2) and ulcer duration (days) at baseline, both logarithmically transformed. Ulcer area and ulcer duration tend to have a skewed distribution and, therefore, a logarithmic transformation is used to obtain a distribution that is closer to the normal. It was initially planned to subsequently test for the inclusion of shared centre frailty effects; however, the final distribution of participants across centres (see *Table 2*) made the frailty model an impractical choice for this analysis. Therefore, only the Kaplan–Meier survival curve, the log-rank test and the Cox's regression model, both unadjusted and adjusted for the logarithm of the area and of the ulcer duration, were undertaken. HRs, corresponding 95% CIs and *p*-values for the model covariates are presented.

Secondary outcomes

Adverse events

Adverse events were reported overall and by trial arm in terms of number of participants with at least one event and total number of events. Serious and non-serious events were presented separately and according to whether or not they were thought to be related or unrelated to treatment. For SAEs, reasons for the serious nature of the events were reported. Differences in total number of events by trial arm were compared using negative binomial regression adjusted for size and duration of ulcer (both log transformed).

Ulcer size

The area resulting from the analysis with the SigmaScan was used in statistical analysis whenever available. In the case when a photograph could not be taken, the measure of the ulcer area was obtained by using the tracing of the ulcer, if available. The area at baseline and at each assessment is summarised using descriptive statistics (mean and SD) for each trial arm and overall. A plot containing means and 95% CIs for both trial arms was also produced with lower confidence limits truncated at zero, as wound area can only be positive.

It was planned a priori that the logarithm of the ulcer area would be investigated via a repeated measures mixed model to see if there were any differences by trial arm; however, owing to the low number of participants and the high number of time points, this model was not judged to be appropriate for the final analysis.

Ulcer recurrence

As a recurrence of the reference ulcer was reported for only two participants, the Cox proportional hazards regression initially planned was not performed. For both participants the number of days from healing to recurrence is presented.

Time to first investigational medicinal product dose

The median time in days from randomisation to date the first IMP dose was taken was presented alongside 95% CI by trial arm and overall.

Time of day

The number of participants who reported taking their study drug in the morning, afternoon and evening is summarised using counts and percentages.

Ulcer pain

The VAS scale [from 0 (no pain) to 100 (worst pain imaginable)] to measure pain was used at baseline and at weeks 4, 5 and 6 in order to increase the likelihood of capture, as not all patients were seen weekly. Only one VAS score was used for the analysis: if the week 5 VAS score was present, this was used; if it was not and either only week 4 or only week 6 were provided, then the corresponding VAS score was used; if both week 4 and week 6 were provided but week 5 was not, then the VAS completed on the closest date to week 5 was taken; if both weeks were completed an equidistance from week 5, then week 4 was taken.

Descriptive statistics of VAS score (mean, SD, median, minimum, maximum, IQR) were calculated overall and for each trial arm at baseline and at week 5, obtained as defined above. A plot of the means and 95% CIs for both trial arms at baseline and at week 5 was produced.

The planned linear regression analysis, aimed to compare differences in pain scores between allocated groups, was not performed owing to low numbers.

Participant compliance with treatment

At each assessment visit, compliance with both the compression therapy (for those receiving this treatment) and with the study capsules was recorded. This was via the following two questions: 'Has the participant complied with their [compression therapy] treatment' (fully/partially/not at all), and 'How often has the participant taken their AVURT capsules (300-mg aspirin/placebo per day) this week?' (every day/most days/some days/not at all). The responses to both of these questions were given numerical values: fully = 1, partially = 2, and not at all = 3; and every day = 1, most days = 2, some days = 3, and not at all = 4. To calculate compliance with compression treatment, the responses across all weeks up to healing/trial exit were summed and divided by the number of visits attended to obtain the mean compliance level for each participant. This compliance level was then categorised as fully compliant if the mean value was 1, partially compliant if the value was between 1 and 3 (not inclusive), and not at all compliant if the value was equal to 3. The number and percentage of participants in each of these categories is presented.

Compliance with study capsules was analysed similarly but only considering responses in the weeks following delivery of the capsules. The compliance level was categorised as fully compliant if the mean value was 1, partially compliant if the value was between 1 and 4 (not inclusive), and not at all compliant if the value was equal to 4. Reasons for lack of full compliance are presented.

The second way that compliance with AVURT capsules was assessed was through the use of the count of the returned capsules at the end of the study. Each participant was given 190 capsules and by subtracting the number of returned pills it was possible to obtain an estimate of the number of capsules actually taken. The number of capsules that should have been taken was calculated starting from the date of first dose until 2 weeks after healing (for those who had healed) or the date of the last visit (for those who did not heal). From this, the percentage of capsules that each participant took (of those they should have taken) was calculated. The level of compliance was split into 11 categories (100%, 90–99%, 80–89%, etc.) and the count and percentage of patients falling in each category is presented (see *Tables 13* and *14*).

Resource use

Level of compression therapy

The number of changes to compression therapy is presented overall and by trial arm, and also stratified by time to healing (or censoring) using the categories 0–2 months, > 2 to 4 months, and > 4 months. The number and percentage of changes to low/medium/high or no compression therapy are presented overall and by trial arm.

Bandaging and hosiery

The number and percentage of changes to each bandage type are presented overall and by trial arm, as are the number and percentage of patients who received each type of bandaging at least once during the study.

Dressing

The number of changes per participant to dressing type is summarised overall and by trial arm, and stratified by time until healing (or censoring) using the categories 0–2 months, > 2 to 4 months, and > 4 months.

The number and percentage of changes to each dressing type are presented overall and by trial arm, as are the number and percentage of patients who received each type of dressing at least once during the study.

Wound consultations

For each participant, the number of wound consultations per week was calculated by summing the number of consultations the participant had in the previous week, declared on the weekly CRFs, plus the visit in which the CRF was completed and dividing it by the number of visits actually attended. The mean number of wound consultations per week is presented alongside SD, median, minimum, maximum and IQR (see *Table 22*).

Approvals obtained and governance

Ethics and Medicines and Healthcare products Regulatory Agency approvals

The trial was approved by Nottingham REC on 29 January 2015 (REC reference number 14/EM/1305) and by the University of York Health Science Research Governance Committee on 16 February 2015. The MHRA approved the study on 26 March 2015 (MHRA reference 16745/0221/001-001). The London Local Research Network completed their global checks on 7 May 2015 and thereafter research governance approval was obtained from each trial centre. The trial was registered with ClinicalTrials.gov and assigned the number NCT02333123, and with the European Clinical Trials Database and assigned the European Clinical Trials Database (EudraCT) number 2014-003979-39.

Trial monitoring

The AVURT was monitored by the sponsor, St George's University of London. The trial was conducted and monitored in compliance with their standard operation procedures:[42] International Conference on Harmonisation Harmonised Tripartite Guidelines For Good Clinical Practice E6 (ICH GCP) and the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/03) (as amended).

The purpose of the monitoring was to ensure:

- the safety and welfare of trial participants
- that trial data were accurate and verified from source data when possible
- that the trial was compliant with good clinical practice and other regulatory requirements.

Trial oversight

The trial was overseen by the TMG, the Trial Steering Committee (TSC) and the DMC.

Trial Management Group

The TMG was responsible for project oversight, directing the management of the trial and reviewing progress. The TMG was chaired by the chief investigator and comprised the trial co-ordinators, trial statisticians and the majority of the coapplicants including a patient representative.

Trial Steering Committee

The TSC provided overall supervision of the progress of the trial towards its interim and overall objectives, to ensure adherence to the protocol and patient safety. The TSC approved the trial protocol prior to participant recruitment, reviewed recruitment, protocol deviations, the trial's results and recommendations made by the DMC.

The TSC was chaired by an independent representative (Professor Julie Brittenden) and membership consisted of three other independent members, a patient representative and members of the research team, including the chief investigator, the sponsor's representative, the trial statistician and trial co-ordinators. The TSC met for the first time prior to participant recruitment and then three times during the course of the trial.

Data Monitoring Committee

The main role of the DMC was to ensure the safety of trial participants, to protect the validity of the trial, to advise the investigators and to make recommendations to the TSC about whether or not the trial should continue. The DMC approved the SAP and reviewed recruitment figures, protocol deviations, protocol amendments and AE data.

The DMC was chaired by an independent representative (Professor Peter Franks) and membership consisted of three other independent members and members of the research team, including the chief investigator, the sponsor's representative, the trial statistician and trial co-ordinators.

Patient and public involvement

At the grant application stage, the views of six patients attending a leg ulcer clinic were elicited. Specifically, they were asked for their views on the likely willingness of patients to take aspirin on a daily basis, given its possible side effects, if it were shown to improve healing of leg ulcers. All responded that they would be willing to take medication if it meant that their ulcer was likely to heal more rapidly. They thought that the risks of aspirin were acceptable given that many patients already take it regularly for cardiovascular disease. In terms of a trial, they thought that they would be happy to receive a dummy tablet (placebo) if it meant that more information could be gleaned about the efficacy of aspirin in terms of healing ulcers – even though a further larger trial might be required to confirm the results. Some patients questioned the benefit about taking a high dose of aspirin. However, the feeling expressed by some was that the perceived increased risks would be worthwhile if it significantly decreased time to healing.

There were two patient coapplicants. Ellie Lindsay, president of the Leg Club Foundation, was a member of the TMG, and our other patient representative, Laurie Williams, was a member of the TSC. Both were involved in the development of the trial during the application stage and throughout the study. They were also involved in the development of the trial's patient information resources.

Protocol amendments

Amendments to the protocol were required by REC prior to approval. Following approval, no substantial amendments were made to the protocol. Details of all ethics and MHRA amendments are detailed in *Appendix 13*.

Chapter 3 Results: feasibility of recruitment

The original participant recruitment window was for 6 months and was due to finish on 30 September 2015. Owing to delays in sites opening and to allow the last few sites to open sufficient time to recruit, this was extended to an 8-month recruitment window. Consequently, to allow the full follow-up of all participants, the total duration of the trial was extended by just over 5 months to 14 December 2016 (the project was originally due to close on 30 June 2016).

Site recruitment

Ten sites opened to recruitment. Prior to recruitment, the sites indicated the approximate number of participants they could recruit (see *Appendix 1*). Recruitment was largely based in leg ulcer community clinics and hospital outpatient clinics. Many of the recruiting sites were chosen as they had been high recruiters to other leg ulcer studies.

Eleven sites were initially interested in participating. Nottingham University Hospitals NHS Trust subsequently declined after undertaking a complete screening review of its patient population, which consisted of 3300 patients referred with chronic oedema of all forms with many suffering from venous leg ulceration. An analysis of their patient profile indicated that they would have little access to non-complex patients. The remaining 10 sites were submitted to REC for approval:

1. St George's Healthcare NHS Trust London
2. Bradford Teaching Hospitals NHS Foundation Trust
3. Leeds Community Healthcare NHS Trust
4. Newcastle upon Tyne Hospitals NHS Foundation Trust
5. Cardiff & Vale University with Aneurin Bevan University Health Board (Newport)
6. Hull and East Yorkshire Hospitals NHS Trust
7. Harrogate and District NHS Foundation Trust
8. Mid Yorkshire Hospitals NHS Trust (Wakefield)
9. Lancashire Care NHS Foundation Trust
10. Sussex Community NHS Trust (Brighton).

Sites were opened throughout the participant recruitment phase and, of these sites, three (Bradford, Leeds and Wakefield) did not open but were in various stages of contracts, training, site initiation visits and approvals when the trial closed to recruitment. During the recruitment phase, we received interest from three other sites that opened after they received REC and local research and development (R&D) approvals: NHS Tayside (Dundee), NHS Lanarkshire and Kent Community Health NHS Foundation Trust. We were also in discussion with Birmingham Community Healthcare NHS Trust towards the end of the recruitment phase.

Barriers to recruitment

The first site opened to recruitment on 23 June 2015, almost 3 months later than scheduled. Barriers to recruitment included a delayed start due to issues releasing the IMP. Because there was uncertainty about when the IMP would be available, we were unable to confirm a start date for recruitment. Sites were expected to recruit their first patient within 35 days of submission of their site specific information forms to their local R&D. Local checks were likely to include the availability of the IMP. Once the IMP had been released, there was a slow rate of sites opening over the summer owing to staff availability at the sites. At three sites key staff were on long-term leave or had left and were waiting for new staff to be appointed before proceeding.

Participant recruitment

Once open to recruitment there were fewer than expected eligible patients at sites. The pre-screening data from sites indicated various and multiple reasons for patients not being approached (*Figure 1*). The main reasons for participant ineligibility were:

- already taking aspirin or other prohibited medication
- having a small or otherwise ineligible ulcer.

In the last few months of recruitment, when all sites were open, the trial was recruiting three to five participants per month (see *Appendix 14*). It was generally thought by some sites that a large proportion of leg ulcer patients were receiving treatment in general practices (i.e. in primary care) or outside primary care in specialist clinics and by district nurses. It was therefore likely that the patients being seen by the secondary recruiting sites were older, more likely to have mixed disease and, therefore, more likely to be already taking aspirin.

Strategies to improve recruitment

Strategies to improve recruitment were explored. Modification of the eligibility criteria was assessed with reference to the pre-screening log data. The only acceptable modification to the exclusion and inclusion criteria was to include a smaller wound size. However, those with a wound area of < 1 cm^2 were excluded, as these ulcers usually heal very rapidly.

In October and November 2015, the chief investigator and a trial manager contacted the recruiting sites that had been the first to open (Kent, Hull, Brighton, Harrogate and Newcastle) to discuss possible solutions to improve participant recruitment. During meetings with sites, a number of ideas were discussed, including:

- Advertising via social media.
- Posters to inform patients about the study.
- Newsletter for sites.
- Flyers for sites to remind staff to recruit to the study.
- Radio advertising (Hull and Harrogate).
- An amendment to protocol to allow participants to visit sites for follow-up purposes (the protocol stated that patients will not be invited to attend clinics for research purposes), and to introduce per-patient payments for visits that were not part of routine care. This was a particular problem for one site (Newcastle) that did not routinely see patients in clinic after their initial visit.
- Allowing for more telephone follow-ups so that participants did not need to come in to clinic as regularly as once per week or once per fortnight.
- Remove minimum ulcer size from the eligibility criteria, in line with the study being conducted in New Zealand.[29]

Apart from removing the minimum ulcer size criterion, each of the options considered would have potentially benefited just one or two of the recruiting sites and, therefore, a variety of strategies would need to be implemented across the trial. The funder and REC had required for regular follow-up to monitor patient safety and, therefore, less frequent follow-up was not viewed as a feasible option by the research team.

A flyer was produced and sent to sites to remind clinic staff to recruit to the trial (December 2015) and three electronic newsletters were sent to sites (two during recruitment, in October 2015 and December 2015) to update on participant recruitment in the trial (the third newsletter was sent in June 2016 after recruitment had closed). The flyer and newsletters were relatively cheap to produce and did not require ethics approval

and so could be sent out swiftly. During training, sites were reminded to identify potential participants before opening so that the participants could be approached as soon as the sites were given the green light to recruit.

Recruitment from primary care

We explored recruitment from primary care, which was supported by the trial's DMC. Two options were considered: to use general practices to identify patients and refer them to the secondary care sites already participating in the study (PICs) or to use general practices as recruitment and treatment centres.

The chief investigator approached the NIHR National Speciality Lead for Primary Care in December 2015 to explore how they might be able to support the study and to request some initial pre-screening to see how many patients could be identified in primary care. The NIHR Clinical Research Network, South London, UK, contacted a number of general practices on our behalf with the trial protocol including the inclusion and exclusion criteria and received three responses:

- One Clinical Commissioning Group provided comments on the difficulty of identifying potential patients using a database search as many of the eligibility criteria, for example size of ulcer and duration of ulcer, are not coded. We were also advised that many patients were taking aspirin over the counter and that this may not currently be recorded in some patients' records.
- Two general practices identified a total of three potential participants in total.

We also approached Clinical Research Network Yorkshire and Humber who ran the trial's inclusion and exclusion criteria through FARSITE (version 0.9.12.2; NorthWest EHealth Limited, Manchester, UK; https://nweh.co.uk/how-we-do-it/our-technology), a web-based anonymous search of patient records. They identified four suitable patients from 12 general practices.

We were unable to obtain details of practice list sizes, Read codes or criteria used in the searches conducted. However, the results indicated that recruitment from primary care was not a viable option using database searches. In addition, two of the recruiting sites (Lanarkshire and Sussex) advised that they would be unable to support referrals from primary care, which at one site was owing to waiting lists already for the service.

Recruitment using general practices as treatment centres was not investigated. Time constraints and budget constraints for implementing this strategy meant that this was option was not explored.

Summary

There were external factors outside the control of the research team that meant that sites were slow to open. Nine out of the 10 recruiting sites were based in secondary care and, once open, there were fewer than anticipated eligible participants. As this was a Clinical Trial of an Investigational Medicinal Product (CTIMP) study, it required more input from a doctor where nurses would otherwise often take the lead. The site make up was very different from other wound trials in which almost all sites were community based with tissue viability nurses acting as principal investigator, which was not possible here. A range of options were considered and explored to improve recruitment, including recruitment from primary care. Preliminary searches of records in primary care also indicated very few potentially eligible participants. In addition, the trial's short recruitment window and budget constraints meant that many of the options considered to improve recruitment were not viable without a funded extension.

Chapter 4 Results

Analyses were conducted following the principles of intention to treat with all events analysed according to the participant's original treatment allocation. Analyses were performed using Stata® version 14 (StataCorp LP, College Station, TX, USA). The trial opened to recruitment on 23 June 2015 and closed to recruitment on 29 February 2016. Participant follow-up was completed on 18 August 2016.

Participant flow

The CONSORT diagrams in *Figures 1* and *2* show the flow of participants pre-screened and the flow of eligible participants during the trial. *Figure 1* illustrates the number of patients pre-screened ($n = 457$) and the number of those who consented ($n = 20$). Pre-screening data were unavailable for the nine remaining patients who consented. Pre-screening was under-reported because some sites did not complete the first pre-screening log. The flow of participants in the trial is illustrated in *Figure 2*, which shows that 29 patients consented. The number of patients randomised by treatment group, receiving the intended treatment, completing the study protocol, and analysed for the primary outcome is presented. Two patients were excluded after they gave consent: one patient developed potential gastric problems and the other patient, affected by multiple comorbidities, was admitted to hospital.

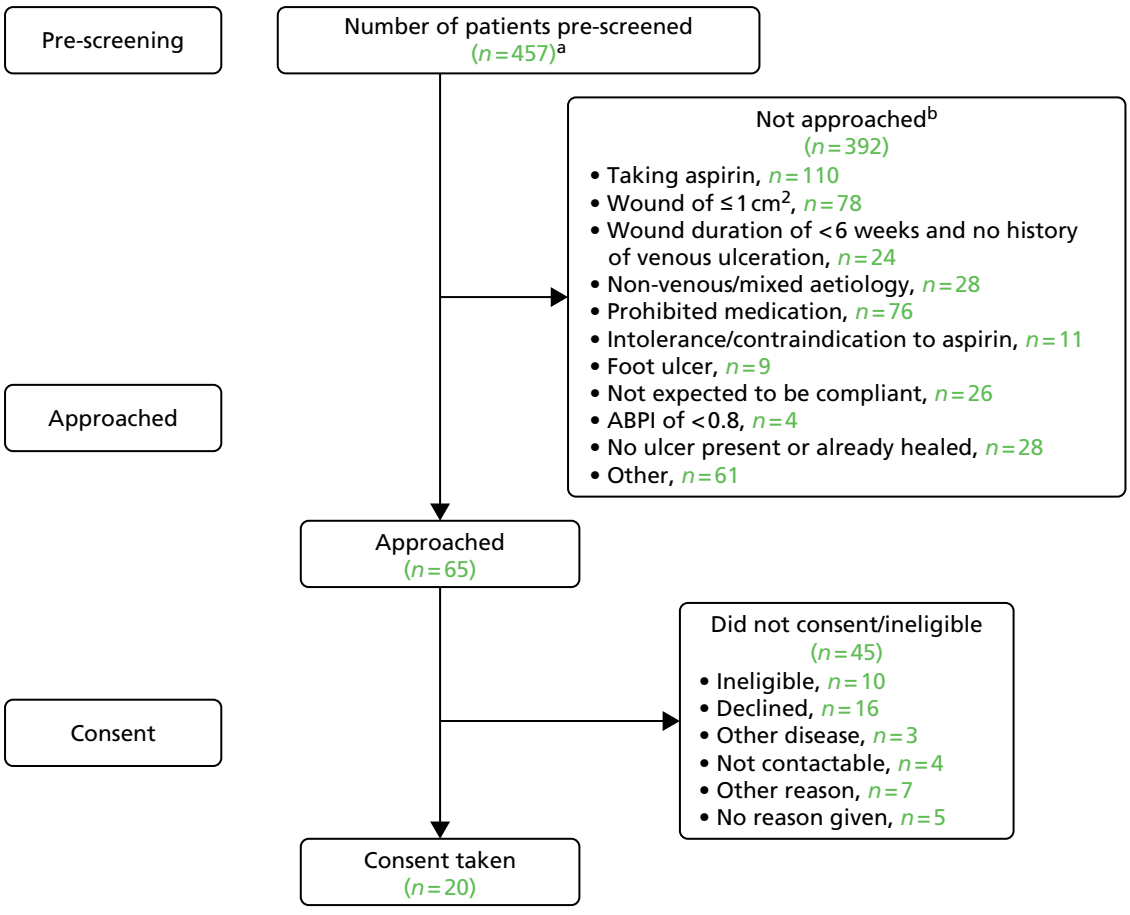

FIGURE 1 The AVURT pre-screening study flow. a, The actual number of patients pre-screened was higher than 457 as the first version of the pre-screening log was not mandatory; and b, reasons not mutually exclusive.

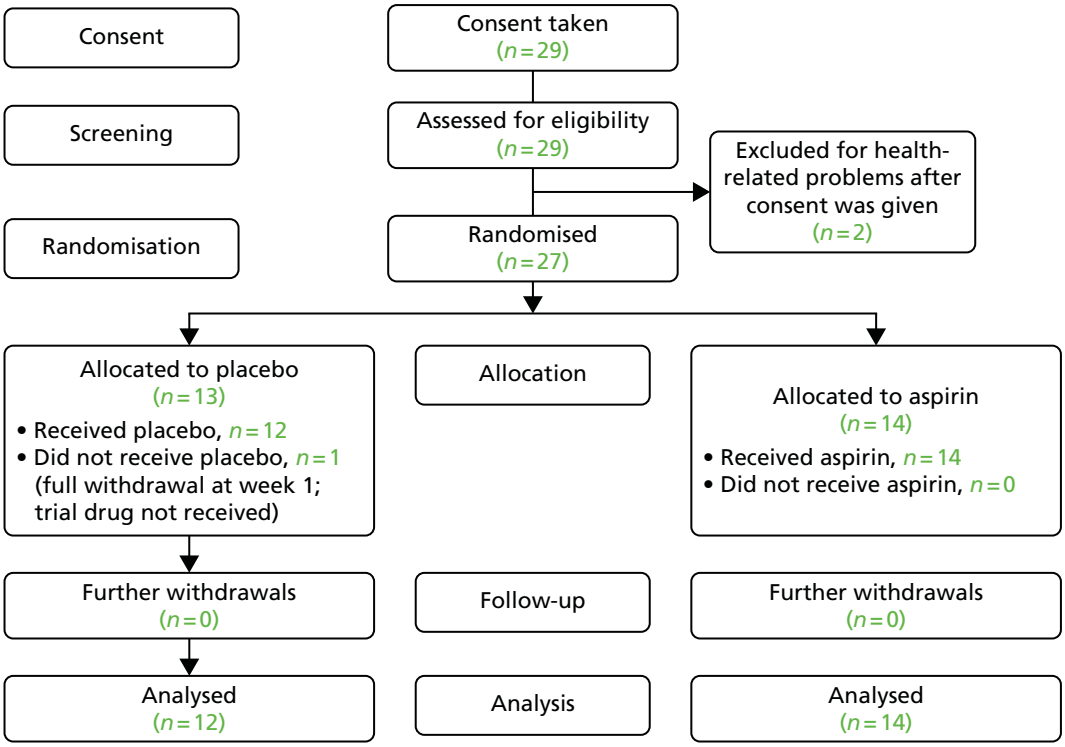

FIGURE 2 The AVURT CONSORT diagram.

Recruitment

Recruitment took place over 8 months, 2 months longer than originally scheduled. The trial opened on 23 June 2015 and the first participant was recruited on 13 July 2015. Recruitment closed on 29 February 2016. In total, 10 sites were opened and eight randomised a total of 27 patients (*Table 2*). The sites in Cardiff and Dundee did not recruit any participants. For accumulative recruitment over time see *Appendix 14*.

Baseline data

The baseline participant and ulcer-related characteristics, as well as the baseline treatments, are shown in *Tables 3–5*. The average age of the 27 randomised participants was 62 years (SD 13 years) and two-thirds were male ($n = 18$). Participants had had their reference ulcer for a median of 15 months and the median size of ulcer was 17.1 cm^2. All participants were receiving compression therapy at baseline.

Withdrawals and losses to follow-up

Withdrawals and losses to follow-up were recorded on a change of status form (see *Appendix 10*, *Form F*) for five patients (placebo, $n = 3$; aspirin, $n = 2$). However, there was only one withdrawal during the course of the study (who was in the placebo group) for whom data on primary outcome was not possible to obtain. This was reported at week 2 and so no follow-up data are available for this participant beyond week 1. The other four participants (placebo, $n = 2$; aspirin, $n = 2$) either agreed to withdraw from treatment but provided full follow-up until week 25 (i.e. the end of planned follow-up) or healed at a point before withdrawal and, thus, all four provided primary outcome data.

Overall, this means that, in terms of analyses related to primary outcome, only one patient was not included (see *Figure 2*).

TABLE 2 Randomised participants by centre

Centre	Participants, *n* (%)
London, St George's	7 (25.9)
Hull and East Yorkshire	6 (22.2)
Newcastle	3 (11.1)
Lancashire	3 (11.1)
Kent	3 (11.1)
Harrogate	2 (7.4)
Brighton	2 (7.4)
Lanarkshire	1 (3.7)
Cardiff	0 (0)
Dundee/Tayside	0 (0)
Total	27 (100.0)

TABLE 3 Baseline data: participant characteristics

	Group		
Participant characteristic	Placebo ($N = 13$)	Aspirin ($N = 14$)	Overall ($N = 27$)
Age (years)			
Mean (SD)	62.1 (15.2)	62.7 (11.6)	62.4 (13.2)
Median (minimum, maximum)	66.6 (38.9, 80.8)	59.2 (47.9, 78.9)	62.0 (38.9, 80.8)
IQR (25%, 75%)	(50.2, 73.4)	(54.0, 74.4)	(50.4, 74.4)
Missing, *n* (%)	0 (0)	0 (0)	0 (0)
Gender, *n* (%)			
Male	7 (53.9)	11 (78.6)	18 (66.7)
Female	6 (46.2)	3 (21.4)	9 (33.3)
Missing	0 (0)	0 (0)	0 (0)
BMI (kg/m^2)			
Mean (SD)	32.1 (8.6)	36.6 (15.0)	34.4 (12.3)
Median (minimum, maximum)	28.4 (19.9, 44.1)	31.6 (20.9, 70.2)	31.5 (19.9, 70.2)
IQR (25%, 75%)	(25.3, 40.6)	(25.9, 40.2)	(25.3, 40.6)
Missing, *n* (%)	0 (0)	0 (0)	0 (0)

continued

TABLE 3 Baseline data: participant characteristics (*continued*)

Participant characteristic	Group		
	Placebo (*N* = 13)	Aspirin (*N* = 14)	Overall (*N* = 27)
Mobility, *n* (%)			
Patient walks freely	10 (76.9)	8 (57.1)	18 (66.7)
Patient walks with difficulty	3 (23.1)	6 (42.9)	9 (33.3)
Patient is immobile	0 (0)	0 (0)	0 (0)
Missing	0 (0)	0 (0)	0 (0)
Ankle mobility of reference leg, *n* (%)			
Patient has full range of motion	7 (53.9)	11 (78.6)	18 (66.7)
Reduced range of ankle motion	6 (46.2)	3 (21.4)	9 (33.3)
Patient's ankle is fixed	0 (0)	0 (0)	0 (0)
Missing	0 (0)	0 (0)	0 (0)
Diabetic, *n* (%)			
Yes[a]	2 (15.4)	3 (21.4)	5 (18.5)
No	11 (84.6)	11 (78.6)	22 (81.5)
Missing	0 (0)	0 (0)	0 (0)
Ethnicity, *n* (%)[b]			
White British	11 (84.6)	12 (85.7)	23 (85.2)
White Irish	1 (7.7)	0 (0)	1 (3.7)
Indian	0 (0)	1 (7.1)	1 (3.7)
Black African	1 (7.7)	1 (7.1)	2 (7.4)
Missing	0 (0)	0 (0)	0 (0)

a All participants with diabetes mellitus had type 2 diabetes mellitus.
b Other categories included on CRF but not ticked: white – other European, any other white background, white and black Caribbean, white and black African, white and Asian, any other mixed background, Pakistani, Bangladeshi, any other Asian background, black Caribbean, any other black background, Chinese, Japanese, and other.

TABLE 4 Baseline data: ulcer related

Ulcer-related characteristic	Group		
	Placebo (*N* = 13)	Aspirin (*N* = 14)	Overall (*N* = 27)
Size of ulcer (cm^2)			
$\leq 5\ cm^2$, *n* (%)	3 (23.1)	3 (21.4)	6 (22.2)
$> 5\ cm^2$, *n* (%)	10 (76.9)	11 (78.6)	21 (77.8)
Mean (SD)	40.7 (55.1)	43.1 (47.6)	42.0 (50.3)
Median (minimum, maximum)	16.0 (2.0, 173.0)	31.3 (3.8, 155.0)	17.1 (2.0, 173.0)
IQR (25%, 75%)	(6.5, 45.0)	(7.0, 45.0)	(6.5, 45.0)
Missing,[a] *n* (%)	0 (0)	0 (0)	0 (0)

TABLE 4 Baseline data: ulcer related (*continued*)

Ulcer-related characteristic	Group		
	Placebo (*N* = 13)	Aspirin (*N* = 14)	Overall (*N* = 27)
Time since first ulcer (months)			
Mean (SD)	112.5 (78.5)	86.4 (86.9)	99.0 (82.4)
Median (minimum, maximum)	101.0 (11.0, 240.0)	48 (2.2, 240.0)	72.0 (2.2, 240.0)
IQR (25%, 75%)	(60.0, 168.0)	(18.0, 192.0)	(19.0, 192.0)
Missing, *n* (%)	0 (0)	0 (0)	0 (0)
Reference ulcer duration (months)			
Mean (SD)	58.6 (73.3)	32.2 (52.0)	44.9 (63.3)
Median (minimum, maximum)	13.0 (4.0, 234.0)	16.5 (1.8, 192.0)	15.0 (1.8, 234.0)
IQR (25%, 75%)	(8.0, 72.0)	(3.5, 24.0)	(6.0, 60.0)
Missing, *n* (%)	0 (0)	0 (0)	0 (0)
Reference leg, *n* (%)			
Left	5 (38.5)	8 (57.1)	13 (48.2)
Right	8 (61.5)	6 (42.9)	14 (51.9)
Missing	0 (0)	0 (0)	0 (0)
Ulcers on reference leg			
Mean (SD)	2.4 (1.7)	2.4 (1.7)	2.4 (1.7)
Median (minimum, maximum)	2.0 (1.0, 7.0)	2.0 (1.0, 6.0)	2.0 (1.0, 7.0)
IQR (25%, 75%)	(1.0, 3.0)	(1.0, 3.0)	(1.0, 3.0)
Missing, *n* (%)	0 (0)	0 (0)	0 (0)
Ulcer episodes on reference leg			
Mean (SD)	1.8 (1.1)	2.3 (1.9)	2.1 (1.5)
Median (minimum, maximum)	1.0 (1.0, 4.0)	1.0 (1.0, 6.0)	1.0 (1.0, 6.0)
IQR (25%, 75%)	(1.0, 2.0)	(1.0, 4.0)	(1.0, 3.0)
Missing, *n* (%)	0 (0)	0 (0)	0 (0)
ABPI			
Mean (SD)	1.1 (0.2)	1.0 (0.1)	1.0 (0.2)
Median (minimum, maximum)	1.0 (0.8, 1.5)	1.0 (0.9, 1.3)	1.0 (0.8, 1.5)
IQR (25%, 75%)	(0.9, 1.2)	(0.9, 1.1)	(0.9, 1.2)
Missing, *n* (%)	2 (15.4)	2 (14.3)	4 (14.8)
Ulcer-related pain (0–100 VAS)[b]			
Mean (SD)	37.7 (25.9)	45.4 (36.0)	41.7 (31.2)
Median (minimum, maximum)	30.0 (5.0, 80.0)	47.5 (0.0, 100.0)	35.0 (0.0, 100.0)
IQR (25%, 75%)	(15.0, 60.0)	(10.0, 70.0)	(10.0, 70.0)
Missing, *n* (%)	0 (0)	0 (0)	0 (0)

a Missing for one patient on baseline CRF, value estimated as agreed a priori from average of reviewed photographs.
b Pain intensity over the last 24 hours (VAS scale: 1–100, in steps of 5).

TABLE 5 Baseline data: compression treatment

Compression treatment characteristic	Group, *n* (%)		
	Placebo (*N* = 13)	Aspirin (*N* = 14)	Overall (*N* = 27)
Level of ankle pressure compression			
Low (≤ 19 mmHg)	0 (0)	0 (0)	0 (0)
Medium (20–39 mmHg)	0 (0)	2 (14.3)	2 (7.4)
High (≥ 40 mmHg)	13 (100)	12 (85.7)	25 (92.6)
Missing	0 (0)	0 (0)	0 (0)
Compression bandaging			
Four layer	6 (46.2)	7 (50.0)	13 (48.2)
Three layer	1 (7.7)	0 (0)	1 (3.7)
Three-layer reduced compression	0 (0)	1 (7.1)	1 (3.7)
Reduced compression	0 (0)	1 (7.1)	1 (3.7)
Two-layer hosiery	2 (15.4)	0 (0)	2 (7.4)
Reduced compression therapy	0 (0)	0 (0)	0 (0)
Other[a]	4 (30.8)	5 (35.7)	9 (33.3)
Missing	0 (0)	0 (0)	0 (0)
Primary dressing			
Silver containing	4 (30.8)	3 (21.4)	7 (26.0)
Iodine containing	2 (15.4)	3 (21.4)	5 (18.5)
Honey containing	0 (0)	1 (7.2)	1 (3.7)
Alginate	1 (7.7)	0 (0)	1 (3.7)
Soft polymer	1 (7.7)	0 (0)	1 (3.7)
Hydrocolloid	0 (0)	2 (14.3)	2 (7.4)
Basic wound contact	3 (23.0)	3 (21.4)	6 (22.2)
Other antimicrobial dressing[b]	1 (7.7)	0 (0)	1 (3.7)
No dressing[c]	1 (7.7)	2 (14.3)	3 (11.1)
Missing	0 (0)	0 (0)	0 (0)

a Actico; full compression (two-layer bandaging k-soft and actico); actico compression 10-cm double spiral as ankle circumference > 25 cm; K two reduced; full compression 30 cm + ankle; short stretch actico; K-Z two-layer compression; single actico – delivers 40 mmHg; Coban 2 layer (full compression).
b Cutimed sorbact.
c Impregnated in coflex bandage.

Primary outcomes

Overall, 13 out of the 26 (50.0%) participants followed up were recorded as healing during the course of the study. All the reference ulcers reported to be healed were later confirmed healed approximately 2 weeks later. The first date of reported healing (as reported on the weekly CRF data collection) was used in the statistical analysis (as per the SAP).

Over the course of the trial, 7 out of 12 participants (58.3%) followed in the placebo group were observed to have a healed reference ulcer, and in the aspirin group the corresponding figure was 6 out of 14 (42.9%). It was not possible to estimate median time to healing and/or corresponding 95% CIs as

< 50% of participants healed during the 25- to 27-week maximum follow-up period of the study (*Table 6*). Therefore, the 25th percentile of time to healing was also estimated. *Figure 3* shows the unadjusted Kaplan–Meier plot of proportion of reference ulcers healed over time. The unadjusted log-rank test investigating the difference between the survival curves showed no statistically significant difference (test statistic = 1.02; $p = 0.30$).

The primary analysis as written in the SAP investigates difference in time to healing using a Cox model adjusting for baseline ulcer area, baseline ulcer duration and centre. The covariates in this model were to be baseline area and duration of the reference ulcer (planned log transformation), randomised allocation and centre as a shared frailty effect. The model was originally chosen with a view to recruiting the target of 100 participants (if successful to follow with a larger definitive study) and was based on analyses performed for the VenUS IV study, which enrolled 457 participants. Given the final distribution of participants across centres (26 participants across eight centres, with six centres contributing three or fewer participants), the shared frailty model is an impractical choice for this analysis. Adjustment with centre as a covariate alongside ulcer area and duration would yield a very low number of events per variable (at approximately four events) and lower than the 10 events that has been previously recommended from simulation studies using Cox regression.[43] Therefore, we present the Kaplan–Meier curves (see *Figure 3*), log-rank test and unadjusted Cox regression as planned but caution against over-interpretation; we also present the results from the Cox regression adjusted for log-area and log-ulcer duration but without adjustment for centre, giving HRs and corresponding 95% CIs (*Table 7*).

TABLE 6 Healing of the reference ulcer (unadjusted analysis)

Outcome	Placebo ($N = 12$)[a]	Aspirin ($N = 14$)	Overall ($N = 26$)
Number healing, *n* (%)	7/12 (58.3)	6/14 (42.9)	13/26 (50.0)
Kaplan–Meier estimate of median time to healing (days) (95% CI)	98 (21 to NE)	NE (84 to NE)	147 (97 to NE)
Kaplan–Meier estimate of 25th percentile time to healing (days) (95% CI)	36 (20 to 97)	111 (69 to NE)	84 (21 to 111)

NE, not possible to estimate.
a One participant was lost to follow-up immediately after randomisation and provided no outcome data.

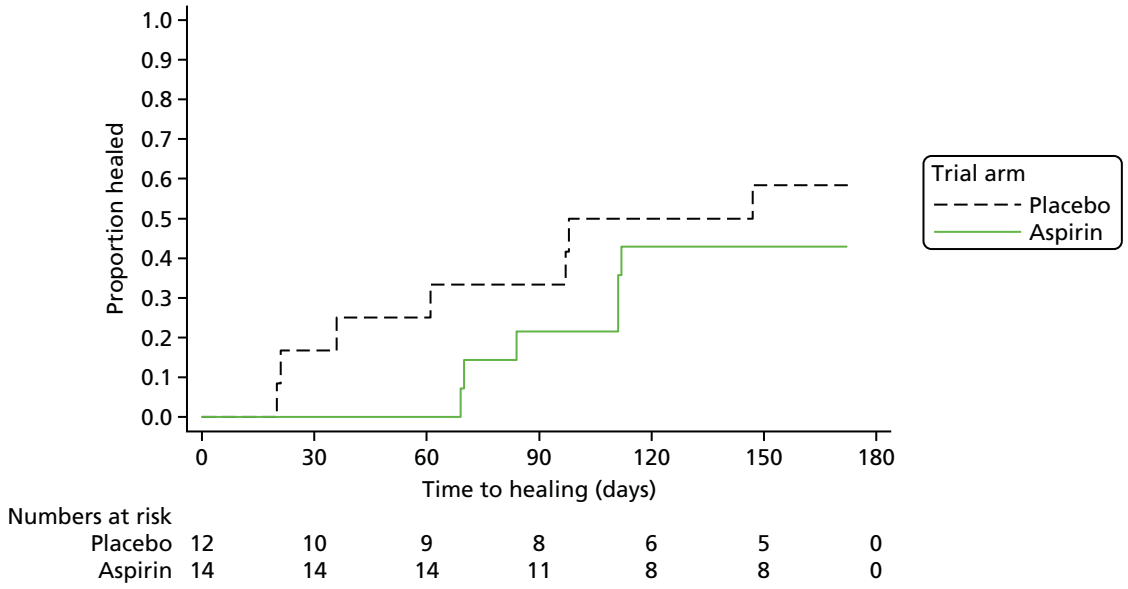

FIGURE 3 Kaplan–Meier plot of time to ulcer healing by trial arm (unadjusted).

TABLE 7 Healing of the reference ulcer (log-rank test, unadjusted and adjusted analysis)

Parameter	HR (95% CI)	*p*-value
Unadjusted Cox regression		
Aspirin vs. placebo (allocation)	0.58 (0.19 to 1.72)	0.322
Adjusted Cox regression		
Aspirin vs. placebo (allocation)	0.58 (0.18 to 1.85)	0.357
Area (log-transformed)	0.42 (0.22 to 0.81)	0.009
Duration (log-transformed)	0.61 (0.34 to 1.08)	0.089

df, degrees of freedom.

Overall, these data do not provide evidence of a difference in time to healing with the addition of aspirin to usual care. The placebo group tended to heal more rapidly but this difference is not statistically significant. The numbers within this feasibility study are small and the results are inconclusive in terms of the primary outcome.

Secondary outcomes

Adverse events

Six out of the 26 (23.1%) participants followed up had no reported AEs (placebo, $n = 3$; aspirin, $n = 3$) and the remaining 20 had AEs (placebo, $n = 9$; aspirin, $n = 11$) (*Table 8*). The total number of events experienced by participants was compared by trial arm adjusting for the prognostic factors (log of baseline reference ulcer area and log of baseline reference ulcer duration) using negative binomial regression as per the SAP. There was no evidence that participants receiving aspirin were more likely to suffer an AE than those receiving placebo (incidence rate ratio 1.31, 95% CI 0.51 to 3.41; $p = 0.58$).

Serious adverse events

One participant suffered one SAE during the course of the study with the description 'blood transfusion for low Hb' [haemoglobin]. This SAE was classified as expected and judged as severe in grade and probably related to the blinded trial treatment (aspirin). This participant had 15 other non-serious AEs, of which two subsequent events were thought to be related to the earlier SAE with descriptions 'colonoscopy: colitis' and 'gastroscopy: stomach ulcer'.

Non-serious adverse events

There were 88 non-serious AEs (placebo, $n = 36$; aspirin, $n = 52$) recorded in total among 20 participants (placebo, $n = 9$; aspirin, $n = 11$).

Ulcer-related pain

The mean baseline VAS score for ulcer-related pain was 37.7 (95% CI 22.0 to 53.4) in the placebo group and was slightly higher at 45.4 (95% CI 24.6 to 66.2) in the aspirin group. At week 5, VAS scores had reduced in both groups with the mean VAS score at week 5 at 13.3 (95% CI 0.3 to 26.3) in the placebo group and 28.5 (95% CI 10.6 to 46.3) in the aspirin group (*Table 9* and *Figure 4*).

TABLE 8 Adverse events

	Group, *n* (%)		
	Placebo (*N* = 12)	Aspirin (*N* = 14)	Overall (*N* = 26)
SAE, *n*	0	1	1
Number of participants with a SAE	0 (0.0)	1 (7.1)	1 (3.8)
Non-serious AEs, *n*	36	52	88
Number of participants with a non-serious AE	9 (75.0)	11 (78.6)	20 (76.9)
Relatedness of non-serious AE to treatment (blinded assessment)			
Not related	21 (58.3)	30 (57.7)	51 (58.0)
Unlikely	1 (2.8)	0 (0)	1 (1.1)
Possibly	7 (19.4)	18 (34.6)	25 (28.4)
Probably	7 (19.4)	4 (7.7)	11 (12.5)
Definitely	0 (0)	0 (0)	0 (0)
Missing	0 (0)	0 (0)	0 (0)
Severity of non-serious AE (blinded assessment)			
Mild	31 (86.1)	44 (84.6)	75 (85.3)
Moderate	3 (8.3)	4 (7.7)	7 (8.0)
Severe	2 (5.6)	4 (7.7)	6 (6.8)
Missing	0 (0)	0 (0)	0 (0)
Total	36 (100.0)	52 (100.0)	88 (100.0)

TABLE 9 Pain at baseline and follow-up

Pain VAS score	Placebo	Aspirin	Overall
Baseline, *n*	13	14	27
Mean (95% CI)	37.7 (22.0 to 53.4)	45.4 (24.6 to 66.2)	41.7 (29.3 to 54.0)
Median (minimum, maximum)	30.0 (5.0, 80.0)	47.5 (0.0, 100.0)	35.0 (0.0, 100.0)
Week 5, *n*	12	13	25[a]
Mean (95% CI)	13.3 (0.3 to 26.3)	28.5 (10.6 to 46.3)	21.2 (10.4 to 32.0)
Median (minimum, maximum)	2.5 (0.0, 60.0)	20.0 (0.0, 75.0)	10.0 (0.0, 75.0)

a VAS score missing for two participants (placebo, *n* = 1; aspirin, *n* = 1) at week 5.

Recurrence

Out of the 13 participants who healed, 12 (92.3%) were assessed for ulcer recurrence using the recurrence assessment form (see *Appendix 10, Form E*), which was completed in the week 25 follow-up. A recurrence was reported for two participants (placebo, *n* = 1; aspirin, *n* = 1). In both cases, the participant was seen in clinic and the ulcer/wound site was clinically assessed. The time in days between ulcer healing and recurrence for these two participants was 126 days (aspirin, healed at week 10) and 158 days (placebo, healed at week 3).

Time to first investigational medicinal product dose

Participants took their first dose of study drug a median of 4 days after randomisation (range 1 to 12 days) (*Table 10*).

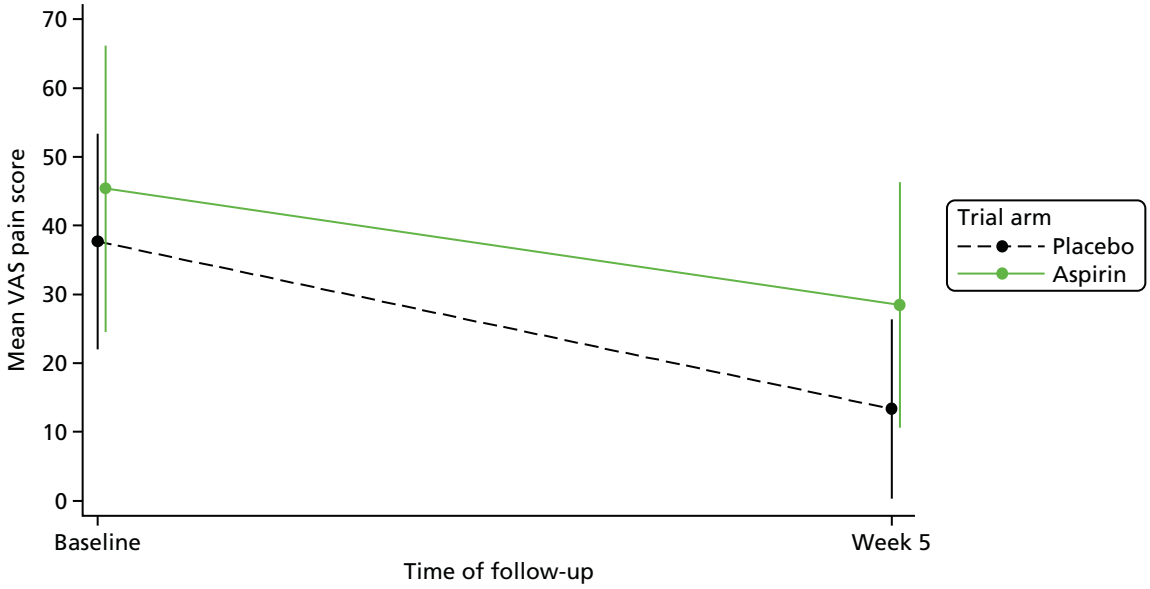

FIGURE 4 Plot of the mean VAS pain score at baseline and at week 5 by trial arm.

TABLE 10 Time to first dose (days)

Time to first dose (days)	Placebo ($n = 12$)	Aspirin ($n = 14$)	Overall ($n = 26$)
Median (minimum, maximum)	3.0 (1.0, 7.0)	4.0 (3.0, 12.0)	4.0 (1.0, 12.0)
95% CI around median	2.0 to 7.0	4.0 to 7.0	3.0 to 6.0

Time of day

The time of day that participants generally took their IMP was recorded for 24 out of the 27 participants randomised (88.9%; placebo, $n = 11$; aspirin, $n = 13$) (*Table 11*). The majority took the IMP in the morning (70.8%; placebo, $n = 9$; aspirin, $n = 8$).

Ulcer area

Seven out of the 27 participants (26%; placebo, $n = 3$; aspirin, $n = 4$) had missing data for baseline ulcer area, as measured by the analysis of a photograph, and so the measure that was calculated manually by the research nurses was used instead for these participants. Photographs were not available for three measurements during follow-up and so the area calculated from tracings was also used in these cases. Participants who healed during the course of the study contributed to the computation of the ulcer area until healing or 2 weeks after healing, according to the availability of an analysable photograph. *Table 12* reports, by trial arm, the number of participants with a valid measure of ulcer area, and the mean and the SD of the ulcer area for each week. The mean ulcer area fluctuates more widely in the placebo group than in the aspirin group (*Figure 5*) with a distinct fortnightly pattern. These fluctuations are caused by two participants who attended their clinic appointments fortnightly and, coincidentally, in the same calendar weeks, and whose

TABLE 11 Time of day of first dose

	Group, *n* (%)		
Time of first dose	Placebo ($N = 11$)	Aspirin ($N = 13$)	Overall ($N = 24$)
Morning	9 (81.8)	8 (61.5)	17 (70.8)
Afternoon	0 (0)	3 (23.1)	3 (12.5)
Evening	2 (18.2)	2 (15.4)	4 (16.7)

TABLE 12 Mean of ulcer area by visit week and allocation group

	Ulcer area (cm^2)					
	Placebo ($N = 13$)		Aspirin ($N = 14$)		Overall ($N = 27$)	
Visit week	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
0	13	39.0 (53.1)	14	33.8 (37.1)	27	36.3 (44.7)
1	9	22.9 (31.2)	11	29.7 (25.4)	20	26.6 (27.6)
2	10	29.8 (43.5)	12	23.8 (19.2)	22	26.5 (31.9)
3	8	15.7 (12.8)	11	39.2 (42.6)	19	29.3 (34.9)
4	10	32.7 (48.4)	10	38.7 (38.9)	20	35.7 (42.8)
5	6	5.9 (7.0)	12	24.9 (24.2)	18	18.6 (21.9)
6	8	32.8 (52.3)	7	28.1 (25.9)	15	30.6 (40.8)
7	5	10.0 (6.9)	10	16.9 (18.6)	15	14.6 (15.7)
8	8	35.1 (53.4)	10	23.3 (14.5)	18	28.5 (36.4)
9	5	7.2 (7.5)	12	22.3 (16.7)	17	17.9 (16.0)
10	9	27.1 (43.8)	12	26.0 (24.9)	21	26.5 (33.3)
11	5	7.3 (7.9)	12	23.6 (24.6)	17	18.8 (22.1)
12	6	37.9 (51.3)	11	26.3 (22.3)	17	30.4 (34.1)
13	3	7.7 (9.5)	11	31.4 (31.0)	14	26.3 (29.3)
14	7	31.7 (42.8)	9	25.2 (22.5)	16	28.1 (31.8)
15	5	7.0 (8.1)	8	25.0 (18.9)	13	18.1 (17.7)
16	5	33.0 (37.1)	9	26.4 (18.6)	14	28.7 (25.5)
17	1	89.2 (.)[a]	8	37.5 (28.8)	9	43.2 (32.0)
18	4	24.2 (22.6)	8	25.8 (19.7)	12	25.2 (19.7)
19	3	14.2 (8.5)	5	27.6 (17.2)	8	22.6 (15.4)
20	4	41.0 (33.7)	6	26.7 (12.2)	10	32.4 (22.7)
21	2	11.5 (10.2)	6	44.8 (31.2)	8	36.5 (30.8)
22	4	39.4 (33.8)	6	22.5 (16.6)	10	29.2 (24.7)
23	2	10.9 (7.9)	7	29.1 (19.3)	9	25.0 (18.7)
24	3	34.9 (43.7)	7	27.3 (20.8)	10	29.6 (27.0)
25	2	12.2 (12.7)	7	33.0 (20.5)	9	28.4 (20.5)
26	0	–	0	–	0	–
27	0	–	1	4.8 (.)[a]	1	4.8 (.)[a]

a No estimate of SD, as data were only available for one participant.

ulcer sizes were particularly large compared with those of the other participants in the placebo group. For example, at baseline, the area of their ulcers was 168 cm^2 and 129 cm^2, while the mean of the ulcer area of the other placebo participants at baseline was 19.1 cm^2 (minimum of 2.14 cm^2 and maximum of 78.0 cm^2). One of these two participants had an ulcer that was extended around the back of the leg, causing difficulties in the estimation of the area. *Figure 6* presents the mean ulcer area over time for the two groups, but with the measurements from these two participants removed.

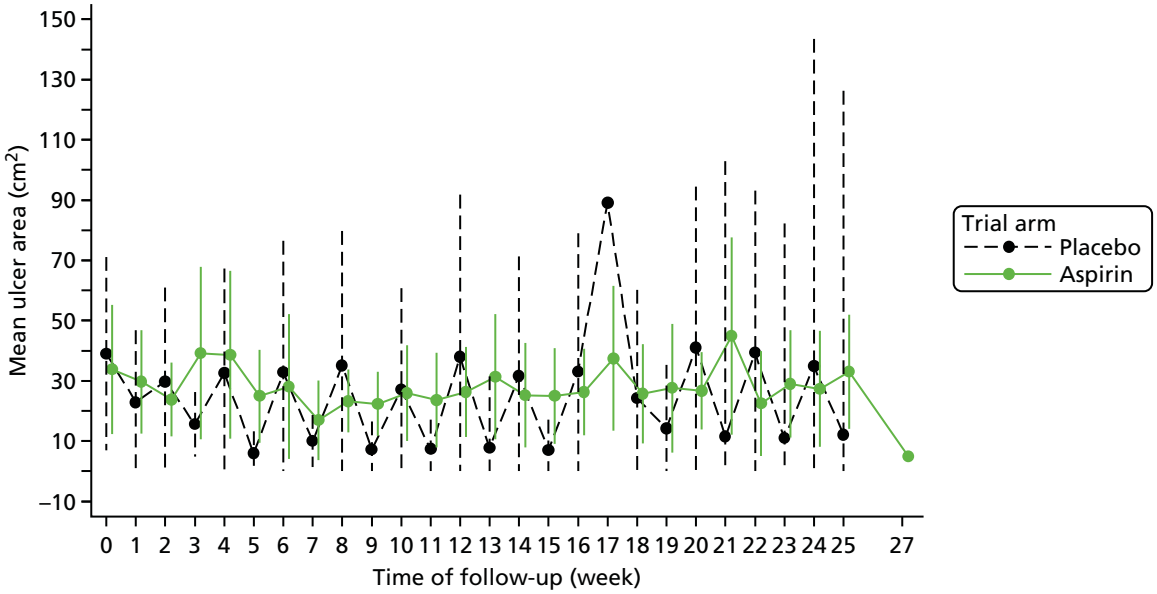

FIGURE 5 Mean of ulcer area and 95% CI for each week of follow-up stratified by allocation group (lower confidence limits truncated at zero).

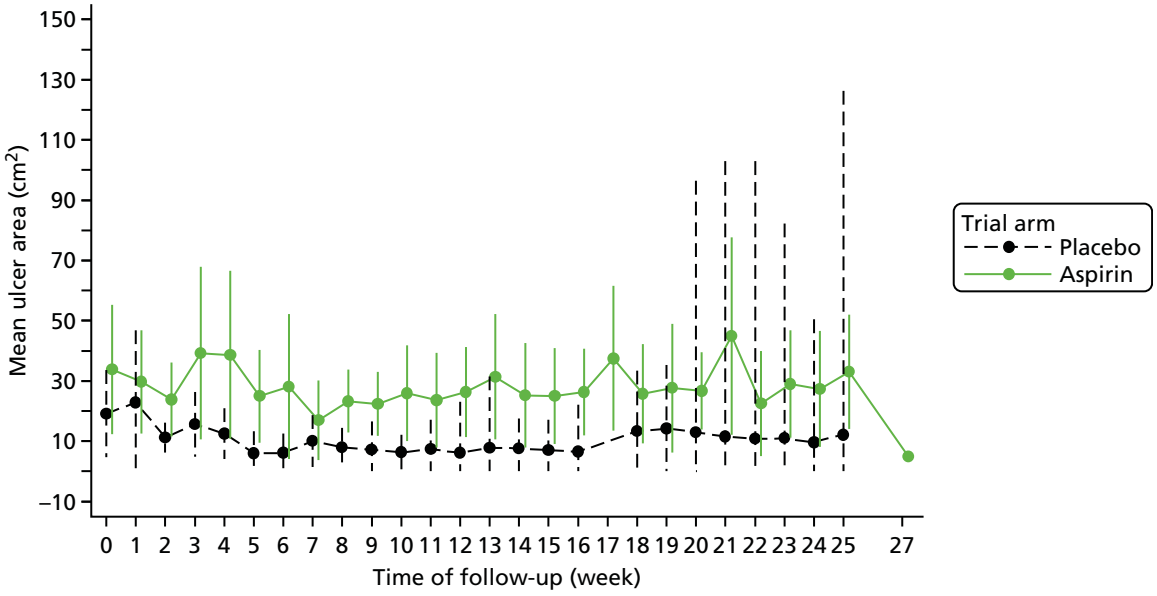

FIGURE 6 Mean of ulcer area and 95% CI for each week of follow-up stratified by allocation group without the two placebo group participants with rather extended ulcers (lower confidence limits truncated at zero).

Compliance

Compliance with compression therapy

The mean number of visits attended up until healing or study exit was 13.3 (SD 7.3) and 17.4 (SD 6.8) in the placebo and aspirin groups, respectively. Ten out of 12 participants (83.3%) in the placebo group and 10 out of 14 participants (71.4%) in the aspirin group were fully compliant with their compression therapy (*Table 13*). Two participants in the placebo group (16.7%) and four participants in the aspirin group (23.1%) were partially compliant. Reasons mentioned by participants for not complying with compression were pain, slipping of the compression bandage, and the participant independently applying the compression garment and, thus, not guaranteeing the correct level of compression. Two of the participants who were classified as partially compliant, one in each group, declared full compliance in half of their visits, while the other four participants did so for at least 89% of their visits.

TABLE 13 Compliance with compression therapy

Compliance with compression therapy	Group, *n* (%)		
	Placebo (*N* = 12)	Aspirin (*N* = 14)	Overall (*N* = 26)
Full compliance	10 (83.3)	10 (71.4)	20 (76.9)
Partial compliance	2 (16.7)	4 (28.6)	6 (23.1)
No compliance at all	0 (0)	0 (0)	0 (0)
Total	12 (100.0)	14 (100.0)	26 (100.0)

Compliance with AVURT capsules

The mean number of visits attended between the administration of the first dose and the date of healing or study exit was 12.8 (SD 7.0) and 17.2 (SD 6.5) in the placebo and aspirin groups, respectively. The imbalance between the groups is probably due to participants in the placebo group healing faster than those in the aspirin group and, therefore, the number of visits in the placebo group is smaller than in the aspirin group.

Eight out of the 12 participants (66.7%) in the placebo group were deemed fully compliant with AVURT capsules and four (33.3%) were partially compliant (*Table 14*). In the aspirin group, 11 out of the 14 participants (78.6%) were deemed fully compliant and three (21.4%) were partially compliant. Among the partially compliant participants, two in the placebo group and two in the aspirin group were fully compliant for at least 88% of their visits. Reasons for not being fully compliant included illness, forgetting to take the capsule and experiencing an AE. The other three participants (placebo, $n = 2$; aspirin, $n = 1$) were deemed to be fully compliant for $\leq 54\%$ of their visits. Two of these participants (placebo, $n = 1$; aspirin, $n = 1$) were withdrawn from treatment at week 8 and week 14, respectively, while one participant (in the placebo group) tended to forget to take the capsule.

Table 15 summarises the level of compliance with the study drug, as assessed by the returned pill count. Ten participants in the placebo group (83.4%) and 10 participants in the aspirin group (71.5%) took at least 90% of the AVURT capsules they should have taken.

Resource use

Resource use: compression therapy

All participants in the placebo group were prescribed high-level compression therapy (≥ 40 mmHg) at baseline. In the aspirin group, 12 were prescribed with high-level compression and two with medium-level compression (20–39 mmHg) (see *Table 5*).

TABLE 14 Compliance with AVURT capsules

Compliance with AVURT capsules	Group, *n* (%)		
	Placebo (*N* = 12)	Aspirin (*N* = 14)	Overall (*N* = 26)
Full compliance	8 (66.7)	11 (78.6)	19 (73.1)
Partial compliance	4 (33.3)	3 (21.4)	7 (26.9)
No compliance at all	0 (0)	0 (0)	0 (0)
Total	12 (100.0)	14 (100.0)	26 (100.0)

TABLE 15 Percentage of AVURT capsules actually taken of those that should have been taken

	Group, *n* (%)		
Percentage	Placebo (*N* = 12)	Aspirin (*N* = 14)	Total (*N* = 26)
100	4 (33.4)	6 (42.9)	10 (38.5)
90–99	6 (50.0)	4 (28.6)	10 (38.5)
80–89	1 (8.3)	–	1 (3.8)
70–79	–	2 (14.3)	2 (7.8)
60–69	–	1 (7.1)	1 (3.8)
50–59	–	–	–
40–49	1 (8.3)	–	1 (3.8)
30–39	–	–	–
20–29	–	1 (7.1)	1 (3.8)
10–19	–	–	–
0–9	–	–	–
Total	12 (100.0)	14 (100.0)	26 (100.0)

The total number of changes to the compression therapy prescribed at baseline during the study was 16, with five changes (31.3%) to a medium compression level and nine changes (56.3%) to a high compression level, one change (6.2%) to a low compression level and one change (6.2%) to no compression at all. In the placebo group, four participants had their level of compression changed: two of them changed from a high level of compression to a higher level, one changed from a medium level to a high level and the fourth participant changed from a high level to a higher level, then to a medium level for 2 weeks and then back to a high level. In the aspirin group, seven participants had their level of compression changed: two participants changed from a high level to a higher level, two changed from a high level to a medium level, one changed from a medium level to a high level, one started with a high level, changed to a medium level for 1 week and then went back to a high level, and one went from a medium level to a low level for 2 weeks, then no compression for 10 weeks and after that back to a high level.

The maximum number of changes to level of compression therapy that a participant had during the follow-up period was three (*Table 16*). Four out of the 12 participants in the placebo group (33.3%) and seven in the aspirin group (50.0%) had at least one change to level of compression therapy; overall, 11 out of the 26 participants (42.3%) had at least one change during their follow-up. The highest number of changes was seen in those participants staying in the study more than 4 months: four out of the six changes (66.7%) in the placebo group and eight out of the 10 changes (80.0%) in the aspirin group were prescribed to participants belonging to this group.

Resource use: compression therapy

Table 17 shows that during the follow-up period, a total of 25 changes to type of compression bandaging were made, 11 (44.0%) in the placebo group and 14 (56.0%) in the aspirin group. Overall, the most frequent changes were to other types of bandaging (32.0%), to three-layer bandaging (20.2%) and to two-layer hosiery bandaging (16.0%).

The four-layer bandaging system was the most frequently used type of compression in this study (*Table 18*), with 16 participants (59.3%) [eight in the placebo group (61.5%) and eight in the aspirin group (57.1%)] receiving it at least once during their follow-up.

TABLE 16 Number of participants per number of changes to compression therapy and period of healing or censoring

Period of healing/censoring (months)	Changes to compression therapy, *n*											
	Placebo (*N* = 12)				Aspirin (*N* = 14)				Total (*N* = 26)			
	0	1	2	3	0	1	2	3	0	1	2	3
0–2	2	2	0	0	0	0	0	0	2	2	0	0
2–4	2	0	0	0	4	2	0	0	6	2	0	0
> 4	4	1	0	1	3	3	1	1	7	4	1	2
Total	8	3	0	1	7	5	1	1	15	8	1	2

TABLE 17 Number and percentage of changes to type of compression therapy

Compression bandaging	Group, *n* (%)		
	Placebo (*N* = 12)	Aspirin (*N* = 14)	Overall (*N* = 26)
Four layer	2 (18.2)	1 (7.1)	3 (12.0)
Three layer	2 (18.2)	3 (21.4)	5 (20.0)
Three-layer reduced compression	0 (0)	1 (7.1)	1 (4.0)
Reduced compression	1 (9.1)	0 (0)	1 (4.0)
Two-layer hosiery	2 (18.2)	2 (14.3)	4 (16.0)
Reduced compression hosiery	1 (9.1)	0 (0)	1 (4.0)
Other[a]	2 (18.2)	6 (43.0)	8 (32.0)
No bandaging	1 (9.1)	1 (7.1)	2 (8.0)
Total number of changes	11 (100.0)	14 (100.0)	25 (100.0)

a k-two layer high compression, actico compression bandaging, k lite k soft clinifast yellow line, juxta compression garment.

TABLE 18 Number and percentage of participants per type of bandaging received at least once

Compression bandaging received at least once, *n* (%)	Placebo (*n* = 13)	Aspirin (*n* = 14)	Overall (*n* = 27)
Four layer	8 (61.5)	8 (57.1)	16 (59.3)
Three layer	2 (15.4)	3 (21.4)	5 (18.5)
Three-layer reduced compression	0 (0)	2 (14.3)	2 (7.4)
Reduced compression	1 (7.7)	1 (7.1)	2 (7.4)
Two-layer hosiery	4 (30.8)	2 (14.3)	6 (22.2)
Reduced compression hosiery	1 (7.7)	0 (0)	1 (3.7)
Other[a]	6 (42.6)	7 (50.0)	13 (48.1)
No bandaging	1 (7.7)	1 (7.1)	2 (7.4)

a Some examples: class 11 stocking (40MM), k-two layer, actico, k lite k soft clinifast yellow line, juxta compression garment, full compression 30 cm + ankle.

Resource use: dressing

The mean number of changes to the type of primary dressing was higher in those participants with a longer follow-up (> 4 months: mean 1.8, SD 2.0) than in participants with a shorter follow-up (≤ 4 months: mean 1.3, SD 1.5); *Table 19*). The mean number of changes to type of dressing per participant during the study was 1.6 (SD 1.8) overall, 1.3 (SD 1.5) for the placebo group and 1.9 (SD 2.0) for the aspirin group.

A total of 41 changes to the primary dressing were recorded during the study (*Table 20*). A total of 15 out of the 41 changes were in the placebo group (36.6%) while the remaining 26 were in the aspirin group (63.4%). Overall, the most frequent changes were to silver-containing dressing (19.5%) and to basic wound contact dressing (19.5%).

Table 21 shows that, overall, silver-containing dressings and basic wound contact were the most widely used types of dressing in this study: 13 out of the 27 participants (48.1%) had a silver-containing dressing at least once during their follow-up, five participants were in the placebo group (38.5%) and eight in the aspirin group (57.1%); 11 participants (40.7%) had basic wound contact dressing at least once, six of them were in the placebo group (46.2%) and five (35.7%) were in the aspirin group.

TABLE 19 Number of changes to primary dressing by period of healing or censoring

	Group		
Number of changes by time period	Placebo ($n = 12$)	Aspirin ($n = 14$)	Overall ($n = 26$)
0–2 months			
Number of participants	4	0	4
Mean (SD)	1.5 (1.0)	–	1.5 (1.0)
Median (minimum, maximum)	1.0 (1.0, 3.0)	–	1.0 (1.0, 3.0)
IQR (25%, 75%)	(1.0, 2.0)	–	(1.0, 2.0)
2–4 months			
Number of participants	2	6	8
Mean (SD)	1.0 (1.4)	1.3 (2.0)	1.3 (1.8)
Median (minimum, maximum)	1.0 (0.0, 2.0)	0.5 (0.0, 5.0)	0.5 (0.0, 5.0)
IQR (25%, 75%)	(0.0, 2.0)	(0.0, 2.0)	(0.0, 2.0)
> 4 months			
Number of participants	6	8	14
Mean (SD)	1.2 (2.0)	2.3 (2.0)	1.8 (2.0)
Median (minimum, maximum)	0.0 (0.0, 5.0)	3.0 (0.0, 5.0)	1.0 (0.0, 5.0)
IQR (25%, 75%)	(0.0, 2.0)	(0.0, 3.5)	(0.0, 3.0)
Whole study period			
Number of participants	12	14	26
Mean (SD)	1.3 (1.5)	1.9 (2.0)	1.6 (1.8)
Median (minimum, maximum)	1.0 (0.0, 5.0)	1.5 (0.0, 5.0)	1.0 (0.0, 5.0)
IQR (25%, 75%)	(0.0, 2.0)	(0.0, 3.0)	(0.0, 3.0)

TABLE 20 Number and percentage of changes to type of dressing

	Group, *n* (%)		
Type of dressing	Placebo (*N* = 12)	Aspirin (*N* = 14)	Overall (*N* = 26)
Basic wound contact	3 (20.0)	5 (19.2)	8 (19.5)
Silver containing	1 (6.7)	7 (26.9)	8 (19.5)
Iodine containing	2 (13.3)	3 (11.5)	5 (12.2)
Hydrocolloid	2 (13.3)	1 (3.8)	3 (7.3)
Alginate	1 (6.7)	1 (3.8)	2 (4.9)
Soft polymer	0 (0)	2 (7.7)	2 (4.9)
Honey containing	0 (0)	1 (3.8)	1 (2.4)
Hydrogel	0 (0)	1 (3.8)	1 (2.4)
Foam	1 (6.7)	0 (0)	1 (2.4)
Film	0 (0)	0 (0)	0 (0)
Other antimicrobial dressing[a]	0 (0)	1 (3.8)	1 (2.4)
Other[b]	2 (13.3)	2 (7.7)	4 (9.8)
No dressing	3 (20.0)	2 (7.7)	5 (12.2)
Total	15 (100.0)	26 (100.0)	41 (100.0)

a Suprasorb + PHMB (polyhexamethylene biguanide) – antimicrobial hydrobalance, cutimed sorbact.
b Promogran, clinisorb, suprasorb X, suprasorb X + PHMB + duodery extra thin hydrocolloid dressing around the edge of the ulcer.

TABLE 21 Number and percentage of participants per type of dressing received at least once

	Group, *n* (%)		
Type of dressing received at least once	Placebo (*N* = 13)	Aspirin (*N* = 14)	Overall (*N* = 27)
Silver containing	5 (38.5)	8 (57.1)	13 (48.1)
Basic wound contact	6 (46.2)	5 (35.7)	11 (40.7)
Iodine containing	3 (23.1)	5 (35.7)	8 (29.6)
Hydrocolloid	1 (7.7)	3 (21.4)	4 (14.8)
Alginate	2 (15.4)	1 (7.1)	3 (11.1)
Honey containing	0 (0)	2 (14.3)	2 (7.4)
Soft polymer	1 (7.7)	1 (7.1)	2 (7.4)
Hydrogel	0 (0)	1 (7.1)	1 (3.7)
Foam	1 (7.7)	0 (0)	1 (3.7)
Film	0 (0)	0 (0)	0 (0)
Other antimicrobial dressing[a]	1 (7.7)	1 (7.1)	1 (3.7)
Other[b]	1 (7.7)	2 (14.3)	3 (11.1)
No dressing	4 (30.8)	4 (28.6)	8 (29.6)

a Suprasorb + PHMB (polyhexamethylene biguanide) – antimicrobial hydrobalance, cutimed sorbact.
b Promogran, clinisorb, suprasorb X, suprasorb X + PHMB + duodery extra thin hydrocolloid dressing around the edge of the ulcer.

Resource use: wound consultations

The mean number of wound consultations per week was 2.1 (SD 1.4) in the placebo group, 1.9 (SD 0.7) in the aspirin group, and 2.0 (SD 1.0) overall (*Table 22*).

Protocol violations or issues that may have an impact on analysis

One participant was unblinded after the trial had completed treatment and analysis was being undertaken. The participant was unblinded via the emergency unblinding procedure after consultation and agreement with the Independent Steering Committees and DMCs. At the time of writing, the TMG has remained blind to this participant's allocation.

No protocol violations were reported.

TABLE 22 Mean number of wound consultations per week

Number of wound consultations per week	Group		
	Placebo ($n = 12$)	Aspirin ($n = 14$)	Overall ($n = 26$)
Mean (SD)	2.1 (1.4)	1.9 (0.7)	2.0 (1.0)
Median (minimum, maximum)	1.9 (1.0, 5.7)	1.9 (1.0, 3.5)	1.9 (1.0, 5.7)
IQR (25%, 75%)	(1.1, 2.0)	(1.6, 2.0)	(1.3, 2.0)

Chapter 5 Discussion

This pilot trial, in which feasibility of recruitment was one of the objectives, was only able to recruit 27% of its target sample size but has important findings for informing the trial design of future CTIMP studies for this patient population.

Summary of findings

Owing to under-recruitment, we were unable to confirm the efficacy of aspirin for VLU healing. Recruitment was more difficult than anticipated owing to the large number of patients already prescribed aspirin medication, predominantly for cardiovascular risk factor management, or who were on concomitant antiplatelet therapies. Others were excluded because they had contraindications to aspirin therapy, had small ulcers of ≤ 1 cm^2 (that were anticipated to heal rapidly) or did not want to be enrolled (frequently reported to be associated with the need for regular clinic attendance).

Participants included in the trial had ulcers of a significantly long duration and may have been considered more difficult to heal. The ulcers that most participants had were large, with 80% of them having a surface area of > 5 cm^2.

The relatively small number of participants recruited to the trial means that any data should be interpreted with caution. There were a large number of AEs during the trial ($n = 89$) with most participants (77%) suffering at least one. The majority of these AEs were non-serious ($n = 88$) and among these 51 (58%) were not related to aspirin. However, there was one SAE of gastrointestinal bleeding requiring blood transfusion. Aspirin was generally well tolerated and there was no evidence of a difference in the number of experienced AEs in the two trial arms.

Compliance with the medication was good, with nearly three-quarters of participants being fully compliant and one-quarter partially compliant. Similarly, the compliance to compression therapy was very good overall and was similar between the treatment groups.

Before study commencement, a decision was made not to collect any data on health-related quality of life and collect only limited resource use health economic data. This was for reasons of brevity and the focus of the trial being feasibility. However, it was hypothesised that participants may receive some benefit in terms of pain relief if they received 300 mg of aspirin daily. The self-reported pain scores at 5 weeks showed no evidence that participants in the aspirin group suffered less pain. The number of clinic visits and dressing/compression changes were also similar among the groups.

The patients taking part in the study tended to have a high BMI, some were experiencing a high degree of ulcer-related pain and the majority receiving high-compression bandaging. A few months into recruitment, and finding that many of the patients were not meeting the trial criteria, we explored recruitment from primary care, which involved a limited database search of records held in primary care. However, very few patients were identified as there were limitations associated with conducting the search on the trial's eligibility criteria. There may have been potentially eligible patients being treated by nurses in general practices. Further investigation of recruitment from primary care was not undertaken owing to time and budget constraints.

Limitations

There are a number of limitations of the trial. Because the trial under recruited (by 73%), some of the pre-planned analyses were infeasible or inappropriate. Because of the low number of participants, for example, the shared centre frailty effects could not be tested and the repeated measures mixed model

for ulcer area could not be estimated. In these cases, the most appropriate analyses were performed. Information concerning compliance with both medication and compression therapy was obtained by participant self-report and pill count.

At the outset of the trial the sponsor did not enforce recruiting sites to record pre-screening log data owing to the disparate nature of the clinics seeing and recruiting patients. It was felt by the sponsor that the heterogeneous nature of the clinics and, therefore, patients would render a pre-screening log meaningless. For example, one site, at St George's, offered a complex wound service led by a vascular surgeon (high prevalence of PAD and very chronic wounds). In contrast, other sites, such as the one in Brighton, were effectively based in the community with a large number of patients with very small and less complex ulcers that were managed solely by nurses. This omission was rectified later but, consequently, the pre-screening data reported is an under-representation of the number of patients screened. It was not possible to conduct second checks of the pre-screening data and there is the possibility of duplicate and incomplete entries. In addition, the data should be interpreted with caution owing to major differences among demographics between some of the recruiting sites.

It is worth reflecting that the relative rates of healing in this study are very far removed from those seen in the earlier UK and Spanish studies,[25,26] which prompted this call for research. One explanation for this may have been the much larger ulcers in this trial or, perhaps, their more chronic nature.

Strengths

Retention and follow-up rates were high and there were few missing data. Both the trial coapplicants and the REC were concerned that participants may suffer a significant number of aspirin-related AEs and SAEs, but this did not appear to be the case. In fact, the number of related events was quite low and the medication appeared to be well tolerated. The frequency of follow-up, once weekly or fortnightly, was to ensure, in part, that information on AEs was identified early (perhaps before progression to more serious AEs). It is possible that some participants suffered other AEs that were related to aspirin, but this seems unlikely given the frequency of assessment.

The aspirin and placebo were manufactured and over-encapsulated effectively in a large capsule. There were some concerns that this may affect participant compliance. However, the sponsor's previous experience with IMP manufacturer and capsule size was reassuring. Indeed, in this trial participant compliance with medication was generally very good and non-compliance was not associated with the size of the capsule.

Data were captured on ulcer area using two formats: paper tracings and digital image analysis. Both of these techniques are supported by published data[3,44] on their reliability and have been used extensively in clinical trials previously. We also decided to use digital image analysis as we thought it may prove easier for the nursing staff. However, many nurses felt more comfortable with wound tracing, especially with the larger ulcers, which may be more difficult to capture in a two-dimensional digital photograph. At the most important time points (baseline and completion of the study), wound tracings were taken to avoid any problems associated with two-dimensional image analysis.

Interpretations

Owing to under-recruitment, we were unable to confirm the effect sizes found in two other published studies, and reliably and confidently establish the safety of aspirin in this population.

It may have been possible to recruit more patients to the trial if other centres could have been rapidly involved. However, the very short nature of the trial meant that it was impossible to involve other centres in a timely fashion.

Generalisability/contribution of this study to the evidence

AVURT was based on plausible results from two other studies investigating aspirin for VLUs.[25,26] This trial has demonstrated that it was possible to randomise those participants who could be recruited, but the study clearly demonstrated that it was not feasible to recruit the necessary participants in the context of a RCT in the UK.

Chapter 6 Conclusions

AVURT was a Phase II randomised pilot trial of aspirin versus placebo for the treatment of patients with chronic venous leg ulceration. It was not possible to recruit the planned number of patients despite an unfunded extension to the trial and, therefore, it can be concluded that a larger Phase III (effectiveness) trial would not be feasible. A future trial would need many centres over a long period of time to get the required numbers if there were no modifications to the inclusion and exclusion criteria.

The Health Technology Assessment (HTA) programme reviewed progress on the study in January 2016 and advised that, in view of the recruitment difficulties that this pilot trial had experienced and was continuing to experience, they did not think it was feasible to recruit the target sample size by the end of July 2016 (the last possible date that participants could be recruited owing to IMP expiry) and, therefore, would not support a funded extension.

There were a number of reasons why patients were excluded or unsuitable for the trial. These included patients with small ulcers at screening and concomitant aspirin therapy (or other concomitant medical therapies that were exclusion criteria). Small ulcers were excluded from the trial because these heal rapidly and the effect of aspirin was unlikely to significantly improve outcome (with potentially increased risks). In retrospect, it may have been possible to randomise patients who were taking 75 mg of aspirin to the larger dose of 300 mg that was used in the trial. However, there are no data (from biological plausibility studies or small trials) to suggest that taking a larger dose of aspirin may have proven effective.

There was a large number of patients already taking aspirin or other antiplatelet medications at screening for cardiovascular indications. It seems likely that this proportion will increase in the future with an ageing population. This suggests that it will likely prove increasingly difficult in the future to recruit to trials of aspirin in patients with chronic venous ulcer of the leg, even if significant changes were made to the present trial design.

The centres recruiting in this trial were identified because they expressed an interest in the trial, estimated that they would be able to recruit sufficient numbers and were the highest recruiters to a previous chronic VLU trial funded by NIHR HTA run through the YTU. The majority of these centres were in a clinic setting (mainly in secondary care locations). It is possible that patients with chronic VLUs are, perhaps increasingly, managed in primary care or in the community. It is also quite possible that younger or fitter patients with easier-to-manage chronic VLUs who may have been eligible for this trial (as they are more likely to have fewer contraindications) were more likely to be managed in the community. Attempts were made to explore recruitment from primary care but this was limited given the relatively short duration of the trial. It is recommended that future studies consider rigorous pre-screening in the design stage of the trial to obtain realistic numbers of potentially eligible patients and to inform recruitment strategy.

Overall, sites found this trial very difficult to recruit to, despite suggesting to the contrary when originally approached. The narrow recruitment window and overall short duration of the trial made it impossible to make changes to the trial recruitment strategies to meet that challenge. The trial's DMC and TSC both requested that it was reported that the commissioned call for AVURT did not allow sufficient time for the trial to be performed. A 6-month recruitment period was not long enough.

AVURT was designed to very carefully identify AEs. The trial applicants and REC were both concerned that AEs may go unnoticed (e.g. mild gastrointestinal side effects leading to potentially life-threatening complications). There were a large number of AEs in the trial, but most were unrelated to the IMP and only one was serious. The overall safety of 300 mg of aspirin once daily in this group of participants would appear to be reasonable (and when a SAE was noted, it was pre-dated by milder gastrointestinal symptoms).

Given these observations, it would appear reasonable to suggest that any further trial of aspirin intervention in chronic VLU might be possible to be performed with fewer clinic visits.

The intervention itself (300 mg of aspirin) appeared feasible and safe in this population but a Phase III RCT would not appear to be feasible in the UK in a hospital clinic-based setting.

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Trial Steering Committee members

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Data Monitoring Committee

We would like to thank external members of the DMC: Professor Peter Franks, Dr Sarah Brown, Mr Jonathan Earnshaw and Mr Toby Richards.

Contributions of authors

Helen Tilbrook (Research Fellow) was the lead study trial co-ordinator. She contributed to the development of the trial protocol and the first draft of the report.

Laura Clark (Research Fellow) contributed to the co-ordination of the study.

Liz Cook (Trial Co-ordinator) contributed to the co-ordination of the study and contributed to the first draft of the report.

Martin Bland (Professor of Health Statistics Emeritus) contributed to the development of the grant application and trial protocol and provided statistical expertise.

Hannah Buckley (Medical Statistician) contributed to the design of the study and wrote the SAP.

Ian Chetter (Associate Dean for Research Hull York Medical School/University of Hull) contributed to the development of the grant application and trial protocol and clinical expertise. Professor Chetter was also a principal investigator.

Jo Dumville (Senior Lecturer in Health Sciences) contributed to the development of the grant application and trial protocol and had project oversight.

Chris Fenner (Core Surgical Trainee) reviewed ulcer photographs and calculated ulcer area.

Rachael Forsythe (Clinical Research Fellow) reviewed ulcer photographs and calculated ulcer area.

Rhian Gabe (Reader in Clinical Trials and Senior Trial Statistician) contributed to the development of the grant application, reviewed the SAP and provided statistical oversight.

Keith Harding (Clinical Lead for Wound Healing) contributed to the development of the grant application and trial protocol and provided clinical expertise.

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Christine Moffatt (Professor of Clinical Nursing Research) contributed to the development of the grant application and trial protocol.

Debbie Rolfe (Acting Head of Research Governance and Regulatory Assurance Manager) was sponsor representative for the study, contributed to the design of the study protocol and was also responsible for project oversight and monitoring of the study.

Illary Sbizzera (Trainee Statistician) undertook the statistical analysis and contributed to the first draft of the report.

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David Torgerson (Director of YTU) provided advice on trial conduct and contributed to the design of the grant application and trial protocol.

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Robert Hinchliffe (Honorary Consultant in Vascular Surgery) lead applicant and chief investigator for AVURT. He had overall responsibility for the design and implementation of the study and the writing of the first draft of the report with final approval of report submission.

All authors contributed to the final manuscript.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Recruiting sites

Site ID	Site	Sources of recruitment	Date open to recruitment	Target	Participants recruited
14	Freeman Hospital, Newcastle upon Tyne	Hospital outpatients within vascular attended by vascular nurses and specialist vascular nurses	23 June 2015	5	3
11	St John's Therapy Centre, London	Hospital outpatient clinic attended by community tissue viability nurses	6 July 2015	12	7
21	Sussex Community NHS Trust, Brighton General Hospital, Brighton	Community leg ulcer clinic	9 July 2015	6	2
17	Hull Royal Infirmary, Hull	Hospital outpatient leg ulcer clinic	10 July 2015	8	6
18	Harrogate District NHS Trust, Harrogate	Hospital outpatient leg ulcer clinic	23 July 2015	4	2
24	Kent Community Health NHS Trust	Wound medicine centres (set-up to treat ambulant patients with long term wounds). Centres overseen by tissue viability nurses	28 September 2015	10	3
22	Monklands Hospital, Lanarkshire	Hospital outpatient leg ulcer clinic	9 October 2015	10	1
15	Wound Healing Research Unit, Cardiff University, Cardiff	General research clinic for wounds within the university	14 October 2015	15–30	0
23	Ninewells Hospital & Medical School, Dundee	Primary care leg ulcer clinic	4 November 2015	5–11	0
20	Lancashire Care NHS Foundation Trust	Community nursing case loads	11 November 2015	4	3
	Total			79–100	27

Appendix 2 Pre-trial screening forms

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AVURT Pre-Screening Log

Study Title: AVURT	Eudract: 2014-003979-39
PI:	Site Name and Number:

Row number	Date pre-screened	Regular concomitant aspirin	Wound smaller than 1cm^2	Ulcer duration less than 6 weeks and no prior history of venous ulceration	Eligible for approach	Patient approached	Reason not approached	Consent	Reason not consented

UNIVERSITY of York

AVURT Pre-Screening Log

Study Title: AVURT	Eudract: 2014-003979-39
PI:	Site Name and Number:

✓= Yes x= No

Row no.	Date pre-screened	Has the patient been pre-screened before? (✓/ x)	Regular concomitant aspirin (✓/ x)	Wound smaller than 1cm² (✓/ x)	Ulcer duration less than 6 weeks and no prior history of venous ulceration (✓/ x)	Eligible for approach (✓/ x)	Patient approached (✓/ x)	Reason not approached	Consent (✓/ x)	Reason not consented

York Trials Unit
AVURT pre screening log v2.0 10.11.15

Appendix 3 Patient information sheet

[Insert Trust/site logo]

INFORMATION SHEET

Study Title: **AVURT: Aspirin for Venous Ulcers Randomised Trial**

Chief Investigator: **Mr Robert Hinchliffe,**
Reader and Honorary Consultant in Vascular Surgery

Invitation to take part in a study:

We would like to invite you to take part in a research study. Before you decide we would like you to understand why the research is being done and what it will involve for you. Please take time to read this information carefully and discuss it with others if you wish. **We will go through the information sheet with you and answer any questions you have.** This should take about 15-20 minutes.

Part 1 of the information sheet tells you the purpose of this study and what will happen to you if you take part.

Part 2 gives you more detailed information about the study.

Please ask us if there is anything that is not clear. Take time to decide whether or not you wish to take part.

Part 1 – The purpose of the study and what will happen to you if you take part.

What is the purpose of the AVURT study?

Compression (leg bandaging or surgical stockings) therapy is the main treatment for venous leg ulcers. However it can be both uncomfortable and inconvenient for everyday life and ulcers may take many months to heal. There is some evidence that taking daily (300mg) aspirin, in addition to compression therapy might improve the healing of venous leg ulcers. But we are not sure that this is true, so further research is required.

[Insert Trust/site logo]

Aspirin is not currently given routinely to patients for leg ulcers, but is commonly used for other conditions and is a cheap drug with relatively few side effects.

In this small study we want to test whether aspirin is better than placebo (dummy medicine) at improving the healing of venous leg ulcers, and if it is safe to use in people with venous leg ulcers. We wish to include 100 patients in the study. If our study shows that taking aspirin could be beneficial we may then decide it is worthwhile carrying out a larger study.

Why have I been invited to take part?

We are inviting patients who have a venous leg ulcer that has been present for more than six weeks, and is larger than 1cm^2, to take part in the study. You will have been invited to take part by a member of your usual medical team or a member of the research team who will also discuss with you what is involved in taking part.

Do I have to take part?

No, it is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw from the study at any time and without giving a reason. A decision not to take part, or to withdraw at any time, will not affect the standard of care you receive now or in the future.

What will happen to me if I take part?

If you choose to take part in the study and sign a consent form:

- You will have information collected about you to confirm that you are suitable for the study.
- You will have your medical history and any medications you are currently taking recorded. A nurse may also ask you to bring in a copy of your prescriptions if you have any.
- It may be necessary for a nurse or the doctor prescribing your study medication to contact your GP to obtain details to check whether you are suitable for the

study. The study doctor may also need to phone you to check your medical history and ask about medications.

- If you are suitable to take part in the study, you will be given either aspirin or a placebo treatment by chance like the flipping of a coin.
- The study medication can be posted to your home or you can collect it from the clinic depending on what is best for you.
- You will have your leg ulcer photographed in order to measure its size at the beginning, as well as during your normal weekly visits to clinic or during home visits over a period of 25 weeks from when you enter the study. If you have more than one leg ulcer, we shall only take a photo of the largest ulcer. In addition you will have a tracing of your ulcer done at the beginning of the study. If photographs cannot be taken then a tracing of the ulcer will be made instead.
- When you get your aspirin or placebo you will be asked to take it once a day for a maximum of 24 weeks. The study medication should be taken with or after food.
- You will be asked about the following during your routine weekly visits: any change to other medications you are taking, such as if you have stopped or have had a medication dose change; whether you have been able to take the trial medication every day as prescribed; and, any change in your health since the previous visit such as headaches or indigestion. If you are male, you will be asked if your partner has become pregnant.
- Your usual nurse or a research nurse will check the size of your ulcer and its healing during the weekly visits.
- If your ulcer has not healed you will also have it traced during your clinic visit or home visit in week 25.
- If your ulcer has healed, you will receive a follow up phone call from your clinic, in week 25, to check if the ulcer has returned.
- During your first and fifth treatment visits you will be asked about the amount of pain you are having from your venous leg ulcer.

[Insert Trust/site logo]

- Your nurse will advise you to stop taking the study medication if your ulcer is confirmed as healed, or if you experience any problems which could be due to the study medication.
- Your participation in the trial will be for 25 weeks unless your ulcer looks like it has healed in week 24 or 25. If this is the case, we would like you to continue in the study for a further two weeks so that we can take weekly photographs of the ulcer, and ask about changes to your medications and to your health since your last visit.
- Your participation in the trial will be for a maximum of 27 weeks.

What do I have to do?

The study will last for 6 months and we want you to:

- Attend your usual leg ulcer clinic regularly /once a week or receive treatment at home as you normally do. If you are unable to attend the clinic or are not seen for a home visit for three consecutive weeks a nurse will phone you to ask about how you have been feeling and about taking the study medication.
- Men and pre-menopausal women will need 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 use of a proprietary spermicidal foam/gel or film; or agree to true abstinence (i.e. withdrawal, calendar, ovulation, and post ovulation are not acceptable methods) from time of consent until 6 weeks after the last dose of the trial medication.
- The study medication can be posted to your home or you can collect it from the clinic depending on what is best for you. If the study medication is posted to your home, we will need you to phone the pharmacy on [redacted] as soon as possible to let them know you have received it.
- Take the study medication (aspirin or placebo) once a day, with or after food, for a maximum of 24 weeks. If your leg ulcer is confirmed as healed before the end of 24 weeks, you will be asked by a member of your medical team to stop taking the medication
- Continue with any other treatment your medical team advises.

[Insert Trust/site logo]

- Complete the study questionnaire at the first visit, around 4 weeks later and one at the end of the study. The questionnaire is very short and the research nurse will help you.
- Provide a pain score at your first visit and 5 weeks after you have started in the study (approximately 4 weeks after receiving your study medication).
- Keep a diary of any changes in any other medication throughout the trial and/or bring in prescriptions on a regular basis.
- Provide information about how you have been feeling especially if you have felt unwell.
- You will also be given a 24 hour contact card with the details of St George's Research Pharmacy. If you feel unwell and require urgent treatment you should use your local NHS services and take the card with you so that a health professional can use it if they need to know which treatment you are receiving in the study.
- If your leg ulcer heals during the study, we will give you a card and a stamped addressed envelope for you to notify the research team if the ulcer breaks down again.
- Return your study medication container and any remaining study medication to the clinic at the end of your participation in the study (25 weeks after you entered the study) or earlier if requested by the research team. If the community nurse visits you at your home please ensure the study medication bottle (complete with intact label) is handed over. The bottle will be returned to the Research Pharmacy at St George's Hospital.

What treatment will I get?

Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (like flipping a coin). You will get one of two treatments.

[Insert Trust/site logo]

Group 1 Aspirin 300mg capsules; **Group 2** Placebo capsules.

One capsule to be taken once every day for a maximum of 24 weeks. The capsule should be taken with or after food. You will be asked to stop taking your study medication before the end of 24 weeks if your leg ulcer is confirmed as healed. Swallow the capsules whole- do not crush or chew. The amount of aspirin is the size of a tablet you might take for a headache.

You will have an equal chance of receiving aspirin or placebo. Neither you, your health care team treating your ulcer or your doctor will know which treatment you are receiving. However, if your doctor needs to find out they can do so.

What are the alternatives for treatment?

The usual option available to you is compression therapy using bandage components or layers wrapped around the leg, or compression hosiery (for example compression stockings). In some cases venous (varicose vein) surgery may be performed. However these options can be uncomfortable, inconvenient for everyday life and take patients many months to heal. In this study we aim to find out if adding daily (300mg) aspirin to compression therapy might improve the healing of venous leg ulcers.

What are the possible benefits of taking part in this study?

If you do take part, you will be contributing to our knowledge about how best to help people with chronic venous leg ulcers. We cannot promise the study will definitely help you as an individual, but we hope that the information and knowledge we get from this study will help improve the treatment of people with venous leg ulcers. If our idea that the addition of aspirin to standard therapy does work, then you could potentially benefit by your ulcer healing faster.

What are the possible disadvantages and risks of taking part?

- You may consider completion of study assessments and taking daily medication as inconvenient.

[Insert Trust/site logo]

- There are some medications that should not be taken with aspirin. There are also medications that require caution when taking aspirin. A nurse will ask about any medications you are currently taking before you start participating in the study, as well as frequently (approximately once a week) during study participation. It is important to let your nurse know about the other medications you are taking; and also to let your doctor or pharmacist know that you are taking aspirin when you get new prescriptions or buy other medications from your pharmacy including herbal and complementary medicines.
- Aspirin is not suitable for people with certain conditions, and sometimes a medicine may only be used if extra care is taken. For these reasons, it is important that your doctor and the research team know of any other medical conditions you might have. Your doctors and research team will check carefully that any other medical conditions you might have should not provide cause for concern.
- If you are pregnant or breastfeeding, considering pregnancy or are not taking adequate contraception you will not be able to take part in this study. For women t is also important during the study to let your doctor and the research team know if you get pregnant, or are trying for a baby. If you become pregnant during this study, then you should stop taking the trial medication immediately. If you or your partner becomes pregnant during the course of the study we will then need to ask you questions about your, your partner's health and your unborn child's health until your baby is born.
- Also tell your doctor and the research team if you have ever had an unusual or allergic-type reaction after taking aspirin or a non-steroidal anti-inflammatory drug (NSAID). NSAIDs include ibuprofen, diclofenac, indomethacin and naproxen.
- You must not take any other preparation which contains aspirin, or any non-steroidal anti-inflammatory painkiller without first seeking the advice of a healthcare professional such as a pharmacist or GP.
- You will not be able to participate in this study if you are currently participating in another study evaluating leg ulcer therapies.

What are the possible side effects of Aspirin?

[Insert Trust/site logo]

Aspirin is generally safe and most people do not have any problems. But like all medicines, it can cause problems among some people. Aspirin has been used for many years and the problems with aspirin are well known to healthcare professionals. We will check regularly about the known problems.

- The common problems include: feeling sick, indigestion and increased risk of bleeding (for example, an increase in the number of nose bleeds, longer bleeding time or bruising more easily). **If you notice any of these problems tell your doctor or nurse**.
- Other problems include the following: difficulty breathing, stomach irritation, stomach ulcers or bleeding which can be severe (you may develop bloody or black tarry stools, severe stomach pain and vomit blood). Inflammation of the liver causing yellowing of the skin or eyes or tiredness, pain in abdomen, joint or muscles may also occur. **If you experience any of these problems STOP taking this medicine and contact a doctor immediately**.
- Aspirin can also cause allergic reactions which may present as blistered skin, swelling of the face, lips, throat or tongue, difficulty breathing, worsening of asthma, shock. There may also be severe rash involving reddening, peeling and swelling of the skin that resembles severe burns; or severe rash, blisters, or red patches on the skin. **If you experience any of these problems STOP taking this medicine and contact your doctor immediately**.

Speak to your doctor or nurse for advice if you experience any other symptoms which you think may be due to your study medication. In this study aspirin is being given for the healing of venous leg ulcers, and not for pain, cardiovascular or other conditions.

Will taking part in this study cost me anything, and will I be paid?

Participation in this study should not cost you anything and there will not be any payment for taking part.

Will my taking part in the study be kept confidential?

Yes, we will follow ethical and legal practice. All identifiable information that is collected about you during this study will be kept confidential and secure, disclosed only to

authorised persons such as researchers, the sponsors (St George's University of London representatives),and regulatory authorities (for the monitoring of the quality and safety of the research). Access to your medical records may also be required for this purpose.

Your name or other directly identifiable information will not appear on any materials produced from this study. You will only be known by a unique trial identification number that will be used on all information collected about you for the purposes of the study. The reports of the research findings may also include anonymised venous leg ulcer photographs from participants who have given permission for their photographs to be used in this way.

Your consent form and questionnaires will be stored confidentially and securely at the clinic you attend. Copies of your trial questionnaires and photos will be sent securely to the University of York's Trials Unit that will be processing the emerging study information. The questionnaires and photos will only include your unique trial identification number and will not contain your name.

Study information sent to the University of York will be held there for a minimum period of 12 month after the end of the study. Following this time period the study information may be transferred to St George's University of London for long term storage.

Will my GP be told of my participation in this study?

Yes, if you agree to take part in this study we will tell your GP. We may also contact your GP about your health when this is necessary during the study.

What happens when the study stops?

You will not be provided with any further study medication once your study participation ends. You will however continue to receive your usual treatment in the normal way.

Part 2- More detailed information about the conduct of the study.

[Insert Trust/site logo]

What if relevant new information becomes available?

If we get new information about the study medication during the study a research doctor or nurse will tell you and discuss whether you should continue in the study. If you decide not to carry on, your care will be continued outside of the study. If you decide to continue in the study you will be asked to sign an updated consent form.

If your research doctor or nurse considers you should not carry on with the study they will explain the reasons to you. If the study is stopped for any other reason, we will tell you. In both situations your care will be continued outside of the study.

What will happen if I don't want to carry on with this study?

Participation in the study is voluntary. You can choose to withdraw from the study at any time.

You may wish to withdraw from the treatment, but continue with the study follow up visits and assessments.

If you choose to also discontinue the follow up visits and assessments, with your permission, we will keep the information that has been collected already but would not collect any more.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer all your questions: contact [Insert names of trial co-ordinators and CI and their contact numbers]

If you wish to complain, or have any concerns about how the study is being carried out, or any other aspects of your care, you may contact:

[INSERT LOCAL INFORMATION, FOR EXAMPLE THE PATIENT ADVICE AND LIAISON SERVICE CONTACT N FORMATION]

[Insert Trust/site logo]

The normal National Health Service complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Sponsor representative at St Georges University of London: [Insert name and contact number]

St Georges, University of London has agreed that if you are harmed as a result of your participation in the study, you will be compensated, provided that, on the balance of probabilities, an injury was caused as a direct result of the intervention or procedures you received during the course of the study. These special compensation arrangements apply where an injury is caused to you that would not have occurred if you were not in the trial. We would not be bound to pay compensation where: The injury resulted from a drug or procedure outside the trial protocol and/or the protocol was not followed. These arrangements do not affect your right to pursue a claim through legal action.

What will happen to the results of the research study?

The results of this study may be published in journals or presented at scientific meetings so other doctors or nurses caring for similar patients can learn from your experience. However, you will not be identified in any reports, publications or presentations. A summary of the results of the study can be sent to you if you like.

Anonymised data that you provide may be used by authorised researchers studying other relevant research projects. Please let us know if you do not agree to this.

Who is organising and funding the research?

St Georges, University of London is the study Sponsor and is taking the overall legal responsibility for the study and will undertake the monitoring and oversight of the participating sites. The study has received funds awarded by the NHS National Institute for Health Research, Health Technology Assessment Programme [grant number NIHR HTA: 13/87/08]

The research team is led by Mr Robert Hinchliffe, Reader in Vascular Sciences and Honorary Consultant in Vascular Surgery, St George's Vascular Institute, St George's

[Insert Trust/site logo]

University of London and St George's Healthcare NHS Trust. The trial is managed by the York Trials Unit at the University of York.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee (REC), to protect your interests. This study has been reviewed and approved by **[Insert name here]** Research Ethics Committee. It has also been reviewed by your local hospital Trust Research and Development Department.

Further Information and Contact Details

If you require further information about this study you can contact the following:

Trial Co-ordinators: [Insert names and contact numbers]

Sponsor Representative: [Insert name and contact number]

If you are unhappy with any aspect of this study, or have any concerns please contact:

Trial Co-ordinators: [Insert names and contact numbers], **or**

Chief Investigator: [Insert name and contact number]

Call the following number Monday – Friday 09:00hrs – 17:25hrs to let the pharmacy know you have received your AVURT study medication: [Insert contact number]

Other useful contact numbers

Your Research Nurse or Nurse

Name: **[Insert site contact details]**

Tel. Number: **[Insert site contact details]**

Appendix 4 Consent form

[Insert Trust/site logo]

Site ID: ☐☐ Screening ID: ☐☐☐☐☐ Participant Trial ID number: ☐☐☐

REC Reference Number: [Insert number here] EudraCT Reference Number: 2014-003979-39

PARTICIPANT CONSENT FORM
AVURT: Aspirin for Venous Ulcers Randomised Trial

Name of Researcher: [Insert name and address of CI]

Please initial each box

1. I confirm that I have read and understand the information sheet dated <to be inserted> version <to be inserted> of the above study and have had the opportunity to consider the information, ask questions and have these answered to my satisfaction. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from the University of York's Trials Unit, St George's University of London (SGUL), NHS Trust or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree to the University of York's Trials Unit holding anonymised copies of study related documents. ☐
5. I understand my GP will be informed of my involvement, and contacted to confirm my eligibility and my health when necessary during the study. ☐
6. **I agree to take part in the above study.** ☐

The statement below can be opted out of and will not affect your participation.

7. I agree to anonymised photographs of my venous leg ulcer being used in publications and other presentations of research findings from the AVURT study. ☐

	day month year	
Name of participant (*please print*)	/ / 2 0 Date	Signature of participant
Name of person taking consent (*please print*)	/ / 2 0 Date	Signature of person taking consent

When completed 1 for patient; 1 for researcher; 1 (original) to be kept with hospital notes

AVURT
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Page 1 of 1

Appendix 5 Screening form

Site ID: ☐☐ Screening ID: ☐☐☐☐☐ Date DD/MM/YY ☐☐☐☐☐☐

AVURT

Aspirin for Venous Ulcers: Randomised Trial

Screening
For Study Investigator Completion

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

I am confident that this information is accurate and complete and I can confirm that the study is being conducted according to protocol and any subsequent amendments and that consent was obtained prior to study entry. Please sign this after the CRF has been completed in full

Signed_____ **(Site Principal Investigator)**

Print_____ **Date signed (DD/MM/YY)** ☐☐ ☐☐ ☐☐

Date informed consent obtained (DD/MM/YY) ☐☐ ☐☐ ☐☐

When completed please fax to York Trials Unit on: [redacted]

Site ID: | | | Screening ID: | | | | | | Date DD/MM/YY | | | | | | |

Instructions for this questionnaire

The following questionnaire contains a series of questions designed to screen patients for participation in the AVURT trial.

Informed consent MUST be obtained prior to any screening procedure, including the completion of this form.

This CRF may be completed by the principal investigator or a delegated member of staff listed on the AVURT Delegation Log. However the details on this form and the eligibility of the patient must be confirmed by the delegated doctor who must sign and date Section G3 of this form and provide their details.

Please complete all sections of the form using the spaces provided and only skip sections if the text directs you to do so.

If the patient is eligible ensure a medically qualified Doctor checks and signs off section G prior to proceeding to AVURT prescribing and randomisation.

If you have further questions please contact a member of the York Trials Unit whose details you will find in the AVURT site information file.

Site ID: ☐☐ Screening ID: ☐☐☐☐☐ Date DD/MM/YY ☐☐☐☐☐☐

Section A: Demographic Data

PERSONAL DETAILS OF PATIENT

1. **Date of birth** DD ☐☐ MM ☐☐ YY ☐☐

2. **Gender** **Male** ☐ **Female** ☐

3. **Has the patient ever smoked?** Never ☐ Current smoker ☐ Previous smoker ☐

SECTION B: Assessment of child bearing potential for MALE and FEMALE participants

1. Is the patient (male or female) of child bearing potential? **Yes** ☐ **No** ☐

A female of child bearing potential is defined as:

- A sexually mature woman (i.e. any woman who has ever experienced menstrual bleeding)
  AND
- Who has not undergone a hysterectomy or who has not been postmenopausal for at least 24 consecutive months (i.e. Who has had menses at any time within the preceding 24 consecutive months)

All males must answer this question

If NO please proceed to Section D

2. If **YES** does the participant agree to use a reliable method of contraception* for the duration of the study and a further six weeks after the last dose of study medication?
   Yes ☐ **No** ☐

*Acceptable methods of contraception are surgical sterilisation, oral, implantable or injectable hormonal method, intrauterine devices or barrier contraceptives

If **NO** the patient is ineligible for participation in AVURT. Please proceed directly to section F and complete

- If YES and Male please proceed straight to section D
- If Yes and Female continue to section C

Site ID: | | | Screening ID: | | | | | | Date DD/MM/YY | | | | | | |

SECTION C: Assessment of breastfeeding FEMALE patients only

1. Is the patient currently breastfeeding? **Yes** ☐ **No** ☐

If **YES** the patient is ineligible for participation in AVURT. Please proceed directly to section F and complete

If **NO** please proceed to section D

SECTION D: Inclusion Criteria

The following criteria MUST all be answered YES for the patient to be included in the trial:		**Yes**	**No**
1	At least one chronic venous leg ulcer - where chronic venous leg ulceration is defined as any break in the skin which 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 purely venous if clinically no other aetiology was suspected. For this the ulcer must be venous in appearance (i.e. moist, shallow, of an irregular shape) and lie wholly or partially within the gaiter region of the leg. If the patient has more than one ulcer we will choose the largest ulcer as the 'index' lesion for purposes of the analysis.		
2	Ulcer area greater than $1cm^2$		
3	Have had an ankle brachial pressure index (ABPI) ≥ 0.8 taken within the previous three months or, where ABPI is incompressible, have had PAD excluded in another form of assessment such as including peripheral pulse examination / toe pressure / duplex ultrasound in combination with clinical judgement to be used to exclude PAD		
4	Aged greater than or equal to 18 years (no upper age limit)		
5	Informed consent		
6	Ulcer duration greater than 6 weeks or prior history of venous ulceration		

Site ID: | | Screening ID: | | | | | | Date DD/MM/YY | | | | | | |

SECTION E: Exclusion Criteria

The following criteria MUST all be answered NO for the patient to be included in the trial:		**Yes**	**No**
1	Unable to provide consent		
2	Unwilling to provide consent		
3	Foot (below the ankle) ulcer		
4	A leg ulcer of non-venous aetiology (e.g. Arterial)		
5	Ankle-brachial pressure index (ABPI) <0.8 or, where ABPI is not compressible, PAD cannot be excluded by other assessments		
6	Regular concomitant aspirin		
7	Previous intolerance of aspirin/contraindication to aspirin (decision made according to the prescribers' clinical judgement)		
8	Is the patient on any prohibited medication: Oral anticoagulants including coumarins (warfarin & acenocoumarol) and phenindione, dabigatran, rivaroxaban and apixaban, heparin, clopidogrel, dipyridamole, probenecid, sulfinpyrazone & iloprost		
9	Known lactose intolerance.		
10	Currently participating in another study evaluating leg ulcer therapies.		
11	Another reason that excluded them from participating within this trial (decision made according to the nurses' or prescribers' clinical judgement)*		
12	Previously been recruited in to this trial.		

*Contraindications to Aspirin as listed on the Aspirin SmPC i.e. Aspirin should not be taken by patients with the following conditions:

- Known hypersensitivity to salicylic acid compounds or prostaglandin synthetase inhibitors (e.g. certain asthma patients who may suffer an attack or faint and certain patients who may suffer from bronchospasm, rhinitis and urticaria) and to any of the excipients;
- Nasal polyps associated with asthma (high risk of severe sensitivity reactions).
- Active or history of recurrent peptic ulcer and/or gastric/intestinal haemorrhage or other kinds of bleeding such as cerebrovascular haemorrhage or a past history of ulceration or dyspepsia.
- Haemorrhagic diathesis; coagulation disorders such as Haemophilia and thrombocytopenia
- Patients who are suffering from gout
- Severe hepatic impairment
- Severe renal impairment

SECTION F: Eligibility

1. Are all the inclusion criteria answered YES (section D)? **Yes** ☐ **No** ☐

2. Are all the exclusion criteria answered NO (section E)? **Yes** ☐ **No** ☐

Site ID: ☐☐ Screening ID: ☐☐☐☐☐ Date DD/MM/YY ☐☐☐☐☐☐

3. Does the participant meet the inclusion criteria in sections B and C **Yes** ☐ **No** ☐

Patient status (please select only one box in this section)

The patient is eligible and will be included in AVURT ☐ please complete all of section G

The patient is not eligible to be included in AVURT ☐ please complete section G1 and G2 then proceed to section H

The patient is eligible but is to be excluded (state why below) ☐ please complete section G1 and G2 then proceed to section H

Site ID: | | Screening ID: | | | | | | Date DD/MM/YY | | | | | | |

SECTION G: Eligibility and medic assessment signoff

1.

	By patient	By Nurse
Consent Form has been signed and dated **(please tick)**		

2. **Form completed by:**

Signature of staff member performing eligibility assessment	
Please print name	
Date	

If ineligible, go to Section H and <u>do not</u> complete question G3 below

Please now pass this form to the named doctor assessor (stated on the delegation log) for their assessment and counter signature, to be completed below, to ensure GCP compliance

3. **Confirmation by doctor assessor**

	Yes	No*
Confirmation AVURT Screening satisfactory		
***If no please specify reasons**		
Baseline Medication Questionnaire checked to ensure inclusion in AVURT study is not contraindicated		
***If no please specify reasons**		

Site ID: | | | Screening ID: | | | | | | Date DD/MM/YY | | | | | | |

Signature of doctor assessor	
Please print name	
Date (DD/MM/YY)	

If the patient is eligible for inclusion in AVURT proceed to randomisation

Instructions to the doctor assessor:

- sign the AVURT prescription and fax to St George's pharmacy [redacted]*
- photocopy the prescription and file in patient notes
- Ensure the original signed prescription is posted to the Sponsor Pharmacy to facilitate release of AVURT study medication to the patient

*NB All AVURT prescribers must be listed on the delegation log copy held with St George's Pharmacy with a sample signature

SECTION H: If patient is not to proceed to AVURT randomisation

- retain this form and return to York trials Unit following the procedure in the AVURT trial file

If the individual(s) completing this screening form has any further comments regarding this screening visit please enter them here:

Appendix 6 Prescription template

[redacted]

AVURT PRESCRIPTION

EudraCT number: 2014-003979-39 *CI:* [redacted]

Patient Name: _____ (Please Print) **Date of Birth:** ____/____/____ (DD/MON/YYYY)

Screening ID: _____ **Site ID:** _____

Drug Allergy: (Please Circle) Yes/ No If YES, please specify: _____

Preferred Delivery Address (Please Print):

_____

_____ Post-Code __ __ __ __ __ __ __

Preferred Delivery Days/Times (Please circle one or all that apply):

Monday Tuesday Wednesday Thursday Friday AM or PM or Both

Ulcer Size: _____ cm^2

Please dispense the following:

ASPIRIN 300mg or PLACEBO capsule

Take ONE capsule ONCE a day with or after food for 24 weeks

Prescriber Signature: _____ **Date:** _____
(As per Delegation Log)
Print Name: _____

Please retain a copy of the prescription, then fax to [redacted] *before sending the original to:*
Research Pharmacy [redacted].

For Pharmacy use only

Patient Trial Number_____ **Bottle Number**_____

Dispensed By: _____ **Date:** _____

Checked By: _____ **Date:** _____

AVURT spread-sheet – info added to 'YORK – AVURT subject update' [redacted]

Version 1.2 Created by: Geoffrey Howell Date: 17th March, 2015
J:\Files\Clinical Trials\Dispensary Trials\AVURT\Prescription V1.2

Appendix 7 Baseline case report form

Site ID: | | | Screening ID: | | | | | | Date (DD/MM/YY) | | | | | | |

AVURT

Aspirin for Venous Ulcers: Randomised Trial

Baseline Questionnaire
For Study Investigator Completion

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

I am confident that this information is accurate and complete and I can confirm that the study is being conducted according to protocol and any subsequent amendments and that consent was obtained prior to study entry. Please sign this after the CRF has been completed in full

Signed_____ **(Site Principal Investigator)**

Print_____

Date (DD.MM.YY)_____

When completed please fax to York Trials Unit, fax no: [redacted]

Site ID: | | | Screening ID: | | | | | | Date (DD/MM/YY) | | | | | | |

Instructions for this questionnaire

This baseline CRF may be completed by the principal investigator or a delegated member of staff listed on the AVURT Delegation Log.

Please complete all sections of this questionnaire putting a cross where applicable, and sign off.

Please also fill in the Baseline Medication CRF in conjunction with this questionnaire

If you have any questions about completing this questionnaire, please contact a member of the York Trials Unit team, whose details you will find in the AVURT site information file.

Site ID: ☐☐ Screening ID: ☐☐☐☐☐ Date (DD/MM/YY) ☐☐☐☐☐☐

LEG ULCER INFORMATION

The reference leg is the leg with the largest ulcer.

1. Please indicate the leg on which the largest eligible ulcer (the reference ulcer) is located (this is called the reference leg)

   Left ☐ Right ☐

2. ABPI of the reference leg ☐.☐☐ date measured ☐☐/☐☐/☐☐

   Unable to take ABPI of the reference leg ☐

3. How long is it approximately since the patient developed their FIRST leg ulcer?

   Years ☐☐ months ☐☐ weeks ☐☐

4. Total number of ulcers on the reference leg ☐

5. Duration approximately of the reference ulcer?

   Years ☐☐ months ☐☐ weeks ☐☐

6. Total number* of ulcer episodes on reference leg including the reference ulcer ☐

***this includes all ulcers that the patient has ever had on the reference leg, both in the past and currently**

MOBILITY

7. Mobility (please cross one box only)

   Patient walks freely ☐
   Patient walks with difficulty ☐
   Patient is immobile ☐

Site ID: ☐☐ Screening ID: ☐☐☐☐☐ Date (DD/MM/YY) ☐☐☐☐☐☐

8. Ankle mobility of reference leg (please cross one box only)

Patient has full range of ankle motion	☐
Patient has reduced range of ankle motion	☐
Patient's ankle is fixed	☐

DIABETES

9. Does the patient have Type I diabetes Yes ☐ No ☐

10. Does the patient have Type II diabetes Yes ☐ No ☐

COMPRESSION AND DRESSINGS

11. What type of compression bandaging does the patient have administered?

If no bandage, please record 'no bandage' under 'other ' below.

Compression bandaging	Select one
Four layer	☐
3 layer	☐
3 layer reduced compression	☐
Reduced compression	☐
2 layer hosiery (aiming to deliver high compression)	☐
Reduced compression hosiery	☐
Other (please state)	

11a. What level of ankle pressure (mm Hg) compression is aimed for ☐☐☐

Site ID: ☐☐ Screening ID: ☐☐☐☐☐ Date (DD/MM/YY) ☐☐☐☐☐☐

12. What is the primary dressing (that is in contact with the ulcer)? Select one in the table below:

If no dressing, please record 'no dressing' under 'other ' below.

Primary dressing	Select one
Silver-containing	☐
Iodine containing	☐
Honey-containing	☐
Alginate	☐
Hydrogel	☐
Soft polymer	☐
Hydrocolloid	☐
Foam	☐
Basic wound contact (absorbent dressing/low adherence dressing)	☐
Film	☐
Other antimicrobial dressing (please state)	
Other (please state)	

HEIGHT AND WEIGHT

13. Patient height : Feet ☐ Inches ☐☐ . ☐☐ **or** cm ☐☐☐ . ☐☐

14. Patient weight : Stones ☐☐ pounds ☐☐ . ☐☐

or kilograms ☐☐☐ . ☐☐

LEG ULCER INFORMATION

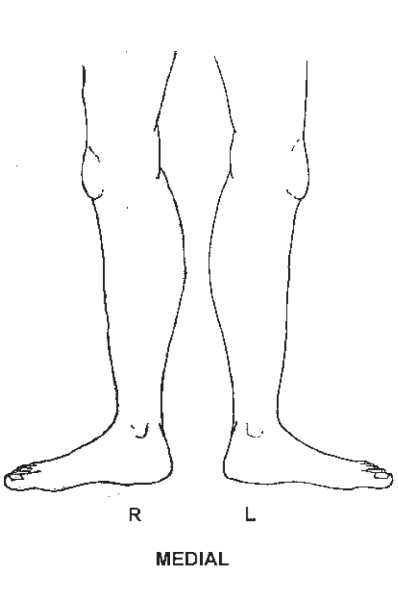
15. Please confirm you have taken a digital photograph of the reference ulcer (largest eligible ulcer) on the reference leg. Yes ☐ No ☐

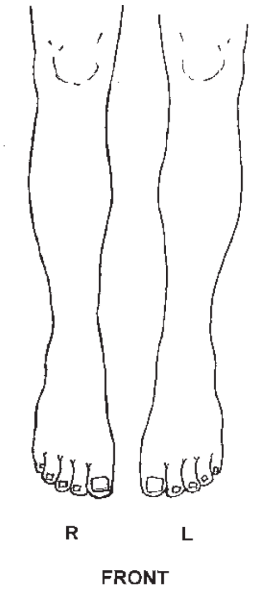
16. Please confirm you have made a tracing of reference ulcer Yes ☐ No ☐

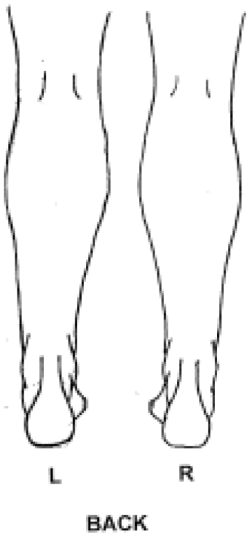
17. Size of reference ☐☐☐.☐☐ cm^2

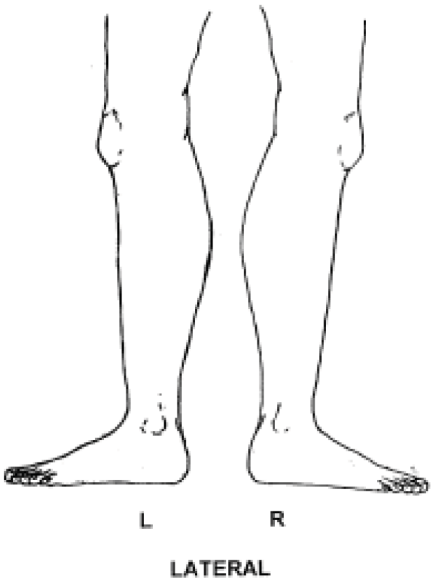
Site ID: | | | Screening ID: | | | | | | Date (DD/MM/YY) | | | | | | |

18. Please draw all leg ulcers on the diagrams below. Clearly indicate the reference ulcer location









Site ID: ☐☐ Screening ID: ☐☐☐☐☐ Date (DD/MM/YY) ☐☐☐☐☐☐

VISUAL ANALOGUE SCORE

19. What is the patients ulcer related pain over the previous 24 hours

Instructions for completing the scale:
Place a cross in one of the boxes below to indicate the intensity of pain from your ulcer(s) over the last 24 hours, ranging from no pain to the worst pain imaginable.

1. **How intense has the pain from your leg ulcer(s) been over the past 24 hours?**

0	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100

No Pain **Worst pain imaginable**

☐☐☐ (For office use only)

20. Confirm the baseline medication questionnaire has been completed Yes ☐ No ☐

21. Which of these best describes the participant's ethnic group? Please tick one box only

White	Mixed	Asian or Asian British	Black or Black British	Chinese, Japanese or other
White British ☐ White Irish ☐ White, other European ☐ Any other White background* ☐	White and Black Caribbean ☐ White and Black African ☐ White and Asian ☐ Any other mixed background* ☐	Indian ☐ Pakistani ☐ Bangladeshi ☐ Any other Asian background* ☐	Black Caribbean ☐ Black African ☐ Any other Black background* ☐	Chinese ☐ Japanese ☐ Other * ☐
If other please specify:				

Site ID: | | | Screening ID: | | | | | | Date (DD/MM/YY) | | | | | | |

_____

Name of person completing form (please print)

_____ _____

Signature of person completing form Date (DD/MM/YY)

Appendix 8 Procedure for taking photographs

AVURT – Trial Procedure

Subject: Digital Photography Procedure

When to take photographs

Photographs of the reference ulcer should be taken every week. (If patients are seen fortnightly, then a photograph should be taken fortnightly.) Also, please take a photograph of the reference ulcer site **when the reference ulcer is first reported as healed, one week later where possible, and a photo 2 weeks later after the first report of healing.** The photo taken 2 weeks after the first report of healing is important as it will be used to confirm whether the ulcer has healed or broken down.

The Camera

Please use the camera supplied for the trial, Nikon Coolpix L31. "All cameras have been calibrated so they are standardised to the same specification – please do not change any of these settings. All cameras have been calibrated to the same specification as follows": [1] Scene auto selector (the icon with the word 'Scene' and image of a heart. This will be displayed on screen when you turn the camera on.) In this mode "the camera responds to the shooting conditions at the time and controls the majority of camera settings." [1] The flash is set to automatic. To use the camera please follow the instructions supplied with the camera.

Taking the photograph

1. Ensure that the ulcer and surrounding area are cleaned thoroughly before taking the photograph.

2. Try to reduce glare and shadow[2].

3. Reference target card – Place reference target card in image. Every digital photograph must include the reference target card, which includes a centimetre measuring scale. The patient's trial number, site id and date must always be clearly written on the reference target card. [There may be a two digit id already pre-printed on the target card, if this number is not your site id, please cross it out and write the correct site ID on the card]. During follow-up please include the week number on the card. To enable us so to distinguish week number from site ID, please use the prefix 'wk', for example, wk 1, wk 2, etc. Please make sure that the reference target card is included in the photograph otherwise the photograph cannot be used.

4. Hold the camera **20 cm, (8 inches), above the ulcer site** (at this distance the reference target card should be legible on screen) and **at "90° above the centre of wound"**[2] – **not at an angle**. **Please do not use zoom function. "**In the case of circumferential wounds additional adjacent photographs may be required. Every reasonable effort must be made to take all consecutive photographs from the same viewpoint and distance,"[1] and using the same trial camera.

5. Ensure that the ulcer is in the **centre** of the screen.

Version 1.0, 19 May 2015
York Trials Unit

"All digital photographs to be kept confidential and secure for the duration of the trial. Patient confidentiality will be maintained throughout trial by the use of unique trial numbers".[1]

"No film, recording media or data to be manipulated or changed in any way with the intention of affecting the results of the trial."[1]

Sending photographs to the YTU

All photographs should be sent to the York Trials Unit (YTU) at the University of York using their electronic Drop Off Service. ***The photographs should be sent as soon as possible after the clinic and no later than a week after the photograph(s) were taken***. The files/photographs must be encrypted before sending them to the YTU. To access the service please go to [redacted]. Drop offs may not exceed 20.0 GB per file, or 20.0 GB total for the entire drop off. If you are not permitted by your site to use this service separate arrangements will be arranged. Contact one of the trial managers if this is the case. "DO NOT COMPRESS PHOTOS."[1] The memory card should hold all the photos that you need to take for the trial. Please do not delete photographs from the memory card until advised to do so by the YTU.

Faults with the camera and collection of cameras at the end of the study

If you camera develops a fault, please report it to the YTU as soon as possible. Please contact [redacted] A replacement camera will be sent to you and we will arrange for the return of the old one.

At the end of the study we will arrange for collection or return of the camera(s).

Procedure adapted from:

[1]Ashby RL, Gabe R, Ali S, Saramago P, Chuang L-H, Adderley U, *et al*. VenUS IV (Venous leg Ulcer Study IV) – compression hosiery compared with compression bandaging in the treatment of venous leg ulcers: a randomised controlled trial, mixed-treatment comparison and decision-analytic model. *Health Technol Assess* 2014;**18**(57)

[2]Bhedi A, Saxena AK, Gadani R, Patel R. Digital photography and transparency –based methods for measuring wound surface area. *Indian J Surg* **75**:111–14

Appendix 9 Medication diary (form completed by participants)

Site ID: | | Date (DD/MM/YY): | | | | | | | Participant ID Number: | | | |

AVURT

Aspirin for Venous Ulcers: Randomised Trial

Participant medication diary
COVER SHEET

For Participant
and
study investigator Completion

AVURT Cover sheet for patient medication diary v1.0 29.05.15
Page 1 of 1

Site ID: ☐☐ Screening ID: ☐☐☐☐☐ Participant ID Number: ☐☐☐

AVURT
Participant Diary- Change in Medication

Baseline Medications – to be filled in with the research nurse at baseline visit

Name of Medication ☐ Reason Taking ☐

How much do you take? ☐ How often do you take it? ☐ Total number of doses daily? ☐

First Dose: Day ☐☐ Month ☐☐ Year ☐☐ Last Dose: Day ☐☐ Month ☐☐ Year ☐☐ or Ongoing? ☐

Name of Medication ☐ Reason Taking ☐

How much do you take? ☐ How often do you take it? ☐ Total number of doses daily? ☐

First Dose: Day ☐☐ Month ☐☐ Year ☐☐ Last Dose: Day ☐☐ Month ☐☐ Year ☐☐ or Ongoing? ☐

Name of Medication ☐ Reason Taking ☐

How much do you take? ☐ How often do you take it? ☐ Total number of doses daily? ☐

First Dose: Day ☐☐ Month ☐☐ Year ☐☐ Last Dose: Day ☐☐ Month ☐☐ Year ☐☐ or Ongoing? ☐

AVURT
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Page 1 of 6

Site ID: Screening ID: Participant ID Number:

Baseline medications continued

Name of Medication **Reason Taking**

How much do you take? **How often do you take it?** **Total number of doses daily?**

First Dose Day Month Year **Last Dose** Day Month Year or **Ongoing?**

Name of Medication **Reason Taking**

How much do you take? **How often do you take it?** **Total number of doses daily?**

First Dose Day Month Year **Last Dose** Day Month Year or **Ongoing?**

Name of Medication **Reason Taking**

How much do you take? **How often do you take it?** **Total number of doses daily?**

First Dose Day Month Year **Last Dose** Day Month Year or **Ongoing?**

AVURT
Version 1.0, 23.04.15
Page 2 of 6

Site ID: Screening ID: Participant ID Number:

Baseline medications continued

Name of Medication **Reason Taking**

How much do you take? **How often do you take it?** **Total number of doses daily?**

First Dose Day Month Year **Last Dose** Day Month Year or **Ongoing?**

Name of Medication **Reason Taking**

How much do you take? **How often do you take it?** **Total number of doses daily?**

First Dose Day Month Year **Last Dose** Day Month Year or **Ongoing?**

Name of Medication **Reason Taking**

How much do you take? **How often do you take it?** **Total number of doses daily?**

First Dose Day Month Year **Last Dose** Day Month Year or **Ongoing?**

Baseline medication

This section to be completed by your nurse or research nurse

____ ______________________

Signature of nurse completing baseline meds Date baseline meds entered

AVURT
Version 1.0, 23.04.15
Page 3 of 6

Site ID: ☐☐ Screening ID: ☐☐☐☐☐ Participant ID Number: ☐☐☐

Changes to Medication

Please record any consistent changes that you or your doctor or nurse make to any of the current medications that you take. Please also record new medications prescribed. You do not need to record if you accidently miss a dose or if you take a different dose on a single occasion.

Name of Medication **Reason Taking (or reason for change)**

How much do you take? **How often do you take it?** **Total number of doses daily?**

	Day	Month	Year		Day	Month	Year		Ongoing?
First Dose	☐☐	☐☐	☐☐	**Last Dose**	☐☐	☐☐	☐☐	**or**	☐

This section to be completed by your nurse or research nurse

_____ _____

Signature of person reviewing change Date reviewed

Name of Medication **Reason Taking (or reason for change)**

How much do you take? **How often do you take it?** **Total number of doses daily?**

	Day	Month	Year		Day	Month	Year		Ongoing?
First Dose	☐☐	☐☐	☐☐	**Last Dose**	☐☐	☐☐	☐☐	**or**	☐

This section to be completed by your nurse or research nurse

_____ _____

Signature of person reviewing change Date reviewed

Site ID: ☐☐ Screening ID: ☐☐☐☐☐ Participant ID Number: ☐☐☐

Name of Medication	Reason Taking (or reason for change)

How much do you take?	How often do you take it?	Total number of doses daily?

	Day	Month	Year		Day	Month	Year		Ongoing?
First Dose	☐☐	☐☐	☐☐	Last Dose	☐☐	☐☐	☐☐	or	☐

This section to be completed by your nurse or research nurse

_____ _____

Signature of person reviewing change Date reviewed

Name of Medication	Reason Taking (or reason for change)

How much do you take?	How often do you take it?	Total number of doses daily?

	Day	Month	Year		Day	Month	Year		Ongoing?
First Dose	☐☐	☐☐	☐☐	Last Dose	☐☐	☐☐	☐☐	or	☐

This section to be completed by your nurse or research nurse

_____ _____

Signature of person reviewing change Date reviewed

Site ID: ☐☐ Screening ID: ☐☐☐☐☐ Participant ID Number: ☐☐☐

Name of Medication **Reason Taking (or reason for change)**

How much do you take? **How often do you take it?** **Total number of doses daily?**

	Day	Month	Year		Day	Month	Year	Ongoing?
First Dose	☐☐	☐☐	☐☐	**Last Dose**	☐☐	☐☐	☐☐	**or** ☐

This section to be completed by your nurse or research nurse

_____ _____

Signature of person reviewing change Date reviewed

Name of Medication **Reason Taking (or reason for change)**

How much do you take? **How often do you take it?** **Total number of doses daily?**

	Day	Month	Year		Day	Month	Year	Ongoing?
First Dose	☐☐	☐☐	☐☐	**Last Dose**	☐☐	☐☐	☐☐	**or** ☐

This section to be completed by your nurse or research nurse

_____ _____

Signature of person reviewing change Date reviewed

Appendix 10 Data collection forms (forms completed by health-care professionals)

Site ID: ☐☐ Date (DD/MM/YY): ☐☐☐☐☐☐ Participant Trial ID Number: ☐☐☐

AVURT

Aspirin for Venous Ulcers: Randomised Trial

Participant 'weekly' data collection file

COVER SHEET

For Study Investigator Completion

1. Date patient was randomised (DD/MM/YY) ☐☐ ☐☐ ☐☐

Signature of nurse completing question 1 (randomisation date)	
Please print name	
Date form completed	

2. Date patient took first dose of IMP (DD/MM/YY) ☐☐ ☐☐ ☐☐

3. What time of day does the participant take their AVURT capsules? *Please circle*

Morning	Afternoon	Evening	Varies

Signature of nurse completing questions 2 and 3.	
Please print name	
Date form completed	

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

AVURT

Aspirin for Venous Ulcers: Randomised Trial

Participant 'weekly' data collection file

For Study Investigator Completion

Week number: 1

If the participant is not seen this week, and therefore you are unable to complete the weekly data collection file, please give reason(s) in the table below and fax this page only alongside Form F, Section 8 and/or the adverse event log if appropriate, to the YTU, Fax number

	Yes	No
1. No scheduled appointment		
2. Participant missed appointment*		
*2a. Was the appointment missed due to an AE or AR that has not been reported previously? **If you answered 'Yes' to this question, please complete Section 8 of this form and the adverse event log**		
*2b Date of missed appointment (DD/MM/YY) ☐☐☐☐☐☐		
3. Change of circumstances **If you answered 'Yes' to this question, please complete form F (Change to study status)**		
4. Other**		
**If other please give reason:		

The nurse completing the above table OR the weekly file to sign here please

Signature of nurse completing form	
Please print name	
Date form completed	

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

Section 1

1. Is the questionnaire being completed (please circle one answer)	
In presence of participant	Over the telephone‡.

‡.If completed over the telephone please go directly to section 2

	Yes	No†
2. Please confirm a photograph of the reference ulcer has been taken		

† If **NO** please trace the ulcer and confirm the ulcer size in cm^2	☐☐☐ . ☐☐ cm^2

Section 2

	Yes	No
1. Has the Reference Ulcer healed?		

If **No** please go to section 3.
If **Yes** please answer questions 1a to 1b and fax this form to York Trials Unit today

Please answer '**Yes**' to one of the following questions.

	Yes	No	
1a. Is this the first appointment that the ulcer has been assessed as healed?			If 'yes' form D to be completed in 2 weeks time*
1b. If you answered 'yes' to question 1a please ensure that form D is to be completed in week no 3			

Section 3

1. How often has the participant taken their AVURT capsules (300mg Aspirin/placebo per day) this week? *(please circle one reason)*			
Every day	Most days	Some days	Not at all

2. If participant has not taken their AVURT capsules each day please record reasons *(please circle all that apply)*					
Illness	Couldn't swallow capsule	Forgot	Couldn't open container	Medic advised to stop taking*	Other**

*Record details of this here	**If other please specify here

If participant has stopped taking medication **due to an adverse reaction please complete section 8 of this form and the adverse event log**

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

Section 4

1. Is the participant currently receiving compression therapy?	**Yes*** ☐ **No** ☐
1a, If **YES***, has the participant complied with their treatment *(please circle one statement below)*	
Fully / Partially* / Not at all*	
*If **partially** or **not at all** please record reason	
2. Has the level of compression changed since the Baseline form was completed?	**Yes*** ☐ **No** ☐

***If YES please complete form A**

Section 5

3. Has the type of primary dressing or bandage changed since the Baseline form was completed?	**Yes*** ☐ **No** ☐

***If YES please complete form B**

Section 6

1. Approximately how many other wound consultations (excluding this one) has the participant had in the last week?	☐
Add additional information (such as if the participant is an inpatient)	

Section 7

1. How many ulcers are present on the REFERENCE LEG	☐

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

Section 8

	Yes	No
1. Has the participant experienced any adverse events		
1a. If yes, was this a serious adverse event (SAE)?		
2. Has the participant experienced any adverse reactions		
2a. If yes, was this a serious adverse reaction (SAR)?		

If YES to any of these questions, please follow the Adverse Event SOP as detailed in the site file
All Adverse Events whether serious or not will be recorded in the clinic notes in the first instance. A record must also be kept in the Sponsor's AE Log JREOLOG0007. SAEs and SARs must be notified to the sponsor immediately when the investigator becomes aware of the event (within 24 hours). Refer to JREOSOP0006 and ensure the completed SAE report form JREODOC0012 is sent to the sponsor via fax on or E-mailed to . **If patients stop taking IMP due to an AE or SAE please complete Form F**

Section 9

	Yes	No
1. Please confirm participant has been asked if there is a change to ANY, medications they take?		■
2. Has there been a change to concomitant medication since baseline questionnaire completion*		
*If **YES please complete Form C ensuring a named doctor is consulted**		

Thank you for completing this form
Please fax to:

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

AVURT

Aspirin for Venous Ulcers: Randomised Trial

Participant 'weekly' data collection file

For Study Investigator Completion

Week number:
2, 3, 7-24, 26,27

If the participant is not seen this week, and therefore you are unable to complete the weekly data collection file, please give reason(s) in the table below and fax this page only alongside Form F, Section 8 and/or the adverse event log if appropriate, to the YTU, Fax number

	Yes	No
1. No scheduled appointment		
2. Participant missed appointment*		
*2a. Was the appointment missed due to an AE or AR that has not been reported previously? **If you answered 'Yes' to this question, please complete Section 8 of this form and the adverse event log**		
*2b Date of missed appointment (DD/MM/YY) ☐☐☐☐☐☐		
3. Change of circumstances **If you answered 'Yes' to this question, please complete form F (Change to study status)**		
4. Other**		
**If other please give reason:		

The nurse completing the above table or the weekly file to sign here please

Signature of nurse completing form	
Please print name	
Date form completed	

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

Section 1

1. Is the questionnaire being completed (please circle one answer)	
In presence of participant	Over the telephone‡

‡If completed over the telephone please go to Section 2

	Yes	No†
2. Please confirm a photograph of the reference ulcer has been taken		

† If **NO** please trace the ulcer and confirm the ulcer size in cm^2	☐☐☐ . ☐☐ cm^2

Section 2

	Yes	No
1. Has the Reference Ulcer healed		

If **NO** please go to Section 3.
If **YES** please answer questions 1a to 1d and fax this form to York Trials Unit today

Please answer **'yes'** to one of the following questions.

	Yes	No	
1a. Is this the first appointment that the ulcer has been assessed as healed?			If 'yes' form D to be completed in 2 weeks time*
1b. Was the ulcer first assessed as healed at last week's appointment?			If 'yes' form D to be completed next week*
1c. Was the ulcer first assessed as healed 2 weeks ago?			If 'yes' form D to be completed today.
			Week no.
1d. If you answered 'yes' to question 1a or 1b please state week number that form D is to be completed			

Section 3

1. How often has the participant taken their AVURT capsules (300mg Aspirin/placebo per day) this week? *(please circle one reason)*			
Every day	Most days	Some days	Not at all

2. If participant has not taken their AVURT capsules each day please record reasons *(please circle all that apply)*					
Illness	Couldn't swallow capsule	Forgot	Couldn't open container	Medic advised to stop taking*	Other**

*Record details of this here	**If other please specify here

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

If participant has stopped taking medication **due to an adverse reaction please complete section 8 of this form and the adverse event log.**

Section 4

1. Is the participant currently receiving compression therapy?	**Yes*** ☐ **No** ☐
1a, If **YES***, has the participant complied with their treatment *(please circle one statement below)*	
Fully / Partially** / Not at all**	
****If partially** or **not at all** please record reason	
2. Has the level of compression changed since this form was last completed?	**Yes*** ☐ **No** ☐

***If YES please complete form A**

Section 5

1. Has the type of primary dressing or bandage changed since this form was last completed?	**Yes*** ☐ **No** ☐

***If YES please complete form B**

Section 6

1. Approximately how many other wound consultations (excluding this one) has the participant had in the last week?	☐
Add additional information (such as if the participant is an inpatient)	

Section 7

1. How many ulcers are present on the REFERENCE LEG	☐

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

Section 8

	Yes	No
1. Has the participant experienced any adverse events that have not been previously reported?		
1a. If yes, was this a serious adverse event (SAE)?		
2. Has the participant experienced any adverse reactions that have not been previously reported?		
2a. If yes, was this a serious adverse reaction (SAR)?		

If YES to any of these questions, please follow the Adverse Event SOP as detailed in the site file All Adverse Events whether serious or not will be recorded in the clinic notes in the first instance. A record must also be kept in the Sponsor's AE Log JREOLOG0007. SAEs and SARs must be notified to the sponsor immediately when the investigator becomes aware of the event (within 24 hours). Refer to JREOSOP0006 and ensure the completed SAE report form JREODOC0012 is sent to the sponsor via fax on or E-mailed to . **If patients stop taking IMP due to an AE or SAE please complete Form F**

Section 9

	Yes	No
1. Please confirm participant has been asked if there is a change to ANY, non-trial, medications they take?		■
2. Has there been a change to concomitant medication since last reported (including doses and frequency of existing medication)?*		
*If **YES please complete Form C ensuring a named doctor is consulted**		

Thank you for completing this form
Please fax to:

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

AVURT

Aspirin for Venous Ulcers: Randomised Trial

Participant 'weekly' data collection file

For Study Investigator Completion

Week number: 4-6

If the participant is not seen this week, and therefore you are unable to complete the weekly data collection file, please give reason(s) in the table below and fax this page only alongside Form F, Section 8 and/or the adverse event log if appropriate, to the YTU, Fax number

	Yes	No
1. No scheduled appointment		
2. Participant missed appointment*		
*2a. Was the appointment missed due to an AE or AR that has not been reported previously? **If you answered 'Yes' to this question, please complete Section 8 of this form and the adverse event log**		
*2b Date of missed appointment (DD/MM/YY) ☐☐☐☐☐☐		
3. Change of circumstances **If you answered 'Yes' to this question, please complete form F (Change to study status)**		
4. Other**		
**If other please give reason:		

The nurse completing the above table or the weekly file to sign here please

Signature of nurse completing form	
Please print name	
Date form completed	

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

Section 1

1. Is the questionnaire being completed (please circle one answer)	
In presence of participant	Over the telephone‡

‡If completed over the telephone please go directly to Section 2

	Yes	No†
2. Please confirm a photograph of the reference ulcer has been taken		

†If **NO** please trace the ulcer and confirm the ulcer size in cm^2	☐☐☐ . ☐☐ cm^2

Section 2

	Yes	No
1. Has the Reference Ulcer healed		

If **NO** please go to section 3.

If **YES** please answer questions 1a to 1d and fax this form to York Trials Unit today

Please answer '**yes**' to one of the following questions.

	Yes	No	
1a. Is this the first appointment that the ulcer has been assessed as healed?			If 'yes' form D to be completed in 2 weeks time*
1b. Was the ulcer first assessed as healed at last week's appointment?			If 'yes' form D to be completed next week*
1c. Was the ulcer first assessed as healed 2 weeks ago?			If 'yes' form D to be completed today.

	Week no.
1d. If you answered 'yes' to question 1a or 1b please state week number that form D is to be completed	

Section 3

1. How often has the participant taken their AVURT capsules (300mg Aspirin/placebo per day) this week? *(please circle one reason)*			
Every day	Most days	Some days	Not at all

2. If participant has not taken their AVURT capsules each day please record reasons *(please circle all that apply)*					
Illness	Couldn't swallow capsule	Forgot	Couldn't open container	Medic advised to stop taking*	Other**

*Record details of this here	**If other please specify here

If participant has stopped taking medication **due to an adverse reaction please complete section 8 of this form and the adverse event log.**

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

Section 4

1. Is the participant currently receiving compression therapy?	**Yes*** ☐ **No** ☐
1a, If **YES***, has the participant complied with their treatment *(please circle one statement below)*	
Fully / Partially* / Not at all*	
*If **partially** or **not at all** please record reason	
2. Has the level of compression changed since this form was last completed?	**Yes*** ☐ **No** ☐

***If YES please complete form A**

Section 5

1. Has the type of primary dressing or bandage changed since this form was last completed?	**Yes*** ☐ **No** ☐

***If YES please complete form B**

Section 6

1. Approximately how many other wound consultations (excluding this one) has the participant had in the last week?	☐
Add additional information (such as if the participant is an inpatient)	

Section 7

1. How many ulcers are present on the REFERENCE LEG	☐

Site ID: | | Date (DD/MM/YY): | | / | | / | | Participant ID No: | | | |

Section 8

	Yes	No
1. Has the participant experienced any adverse events that have not been previously reported?		
1a. If yes, was this a serious adverse event (SAE)?		
2. Has the participant experienced any adverse reactions that have not been previously reported?		
2a. If yes, was this a serious adverse reaction (SAR)?		

If YES to any of these questions, please follow the Adverse Event SOP as detailed in the site file
All Adverse Events whether serious or not will be recorded in the clinic notes in the first instance. A record must also be kept in the Sponsor's AE Log JREOLOG0007. SAEs and SARs must be notified to the sponsor immediately when the investigator becomes aware of the event (within 24 hours). Refer to JREOSOP0006 and ensure the completed SAE report form JREODOC0012 is sent to the sponsor via fax on or E-mailed to . **If patients stop taking IMP due to an AE or SAE please complete Form F**

Section 9

	Yes	No
1. Please confirm participant has been asked if there is a change to ANY, non-trial, medications they take?		
2. Has there been a change to concomitant medication since last reported (including doses and frequency of existing medication)?*		
*If **YES please complete Form C ensuring a named doctor is consulted**		

Section 10

Visual Analogue Score

Instructions for completing the scale:
Place a cross in one of the boxes below to indicate the intensity of pain from your ulcer(s) over the last 24 hours, ranging from no pain to the worst pain imaginable.

1. How intense has the pain from your leg ulcer(s) been over the past 24 hours ?

0	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100

No Pain **Worst pain imaginable**

			(For office use only)

Thank you for completing this form
Please fax to:

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

AVURT

Aspirin for Venous Ulcers: Randomised Trial

Participant 'weekly' data collection file

For Study Investigator Completion

Week number: 25

If the participant is not seen this week, and therefore you are unable to complete the weekly data collection file, please give reason(s) in the table below and fax this page only alongside Form F, Section 8 and/or the adverse event log if appropriate, to the YTU, Fax number

	Yes	No
1. No scheduled appointment		
2. Participant missed appointment*		
*2a. Was the appointment missed due to an AE or AR that has not been reported previously? **If you answered 'Yes' to this question, please complete Section 8 of this form and the adverse event log**		
*2b Date of missed appointment (DD/MM/YY) ☐☐☐☐☐☐		
3. Change of circumstances **If you answered 'Yes' to this question, please complete form F (Change to study status)**		
4. Other**		
**If other please give reason:		

The nurse completing the above table OR the weekly file to sign here please

Signature of nurse completing form	
Please print name	
Date form completed	

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

Section 1

1. Is the questionnaire being completed (please circle one answer)	
In presence of participant	Over the telephone‡

‡If completed over the telephone please go directly to Section 2

	Yes	No
2. Please confirm a photograph of the reference ulcer has been taken		

3. Please trace the ulcer and confirm the ulcer size in cm^2	☐☐☐ . ☐☐ cm^2

Section 2

	Yes	No
1. Has the Reference Ulcer healed		

If **NO** please go to Section 3.
If **YES** please answer questions 1a to 1d and fax this form to York Trials Unit today

Please answer '**yes**' to one of the following questions.

	Yes	No	
1a. Is this the first appointment that the ulcer has been assessed as healed?			If 'yes' form D to be completed in 2 weeks time*
1b. Was the ulcer first assessed as healed at last week's appointment?			If 'yes' form D to be completed next week*
1c. Was the ulcer first assessed as healed 2 weeks ago?			If 'yes' form D to be completed today.

	Week no.
1d. If you answered 'yes' to question 1a or 1b please state week number that form D is to be completed	

Section 3

1. How often has the participant taken their AVURT capsules (300mg Aspirin/placebo per day) this week? *(please circle one reason)*			
Every day	Most days	Some days	Not at all

2. If participant has not taken their AVURT capsules each day please record reasons *(please circle all that apply)*					
Illness	Couldn't swallow capsule	Forgot	Couldn't open container	Medic advised to stop taking*	Other**

*Record details of this here	**If other please specify here

If participant has stopped taking medication **due to an adverse reaction please complete section 8 of this form and the adverse event log.**

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

Section 4

1. Is the participant currently receiving compression therapy?	**Yes*** ☐ **No** ☐
1a, If **YES***, has the participant complied with their treatment *(please circle one statement below)*	
Fully / Partially* / Not at all*	
*If **partially** or **not at all** please record reason	
2. Has the level of compression changed since this form was last completed?	**Yes*** ☐ **No** ☐

***If YES please complete form A**

Section 5

1. Has the type of primary dressing or bandage changed since this form was last completed?	**Yes*** ☐ **No** ☐

***If YES please complete form B**

Section 6

1. Approximately how many other wound consultations (excluding this one) has the participant had in the last week?	☐
Add additional information (such as if the participant is an inpatient)	

Section 7

1. How many ulcers are present on the REFERENCE LEG	☐

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

Section 8

	Yes	No
1. Has the participant experienced any adverse events that have not been previously reported?		
1a. If yes, was this a serious adverse event (SAE)?		
2. Has the participant experienced any adverse reactions that have not been previously reported?		
2a. If yes, was this a serious adverse reaction (SAR)?		

If YES to any of these questions, please follow the Adverse Event SOP as detailed in the site file
All Adverse Events whether serious or not will be recorded in the clinic notes in the first instance. A record must also be kept in the Sponsor's AE Log JREOLOG0007. SAEs and SARs must be notified to the sponsor immediately when the investigator becomes aware of the event (within 24 hours). Refer to JREOSOP0006 and ensure the completed SAE report form JREODOC0012 is sent to the sponsor via fax on or E-mailed to . **If patients stop taking IMP due to an AE or SAE please complete Form F**

Section 9

	Yes	No
1. Please confirm participant has been asked if there is a change to ANY, non-trial, medications they take?		
2. Has there been a change to concomitant medication since last reported (including doses and frequency of existing medication)?*		
*If **YES please complete Form C ensuring a named doctor is consulted**		

At week 25 please collect the AVURT medication from the participant. Return this medication to St Georges pharmacy

Thank you for completing this form
Please fax to:

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

AVURT: Form A
Changes to compression therapy

Week number: ☐

Date of completion
Day Month Year
☐☐ ☐☐ ☐☐

What level of compression is the new treatment aiming for? *Please tick*

Low ≤19mmHG	Medium 20-39mmHG	High 40mmHG & above	None

Signature of nurse filling in form A	
Please print name	
Date (DD/MM/YY)	

Please fax to York Trials Unit on:
[redacted]

AVURT Data Collection File Form A
Version 1.1 09.06.15

Page 1 of 1

Site ID: ☐☐ Date (DD/MM/YY): ☐☐/☐☐/☐☐ Participant ID No: ☐☐☐

AVURT: Form B
Changes to dressing or bandages Page 1 of 2

Week number: ☐

Date of completion
Day Month Year
☐☐ ☐☐ ☐☐

1. What is the primary dressing (that is in contact with the ulcer)? Select one in the table below

If no dressing, please state 'no dressing' in 'other' box below

New Dressing	Select one
Silver-containing	
Iodine-containing	
Honey-containing	
Alginate	
Hydrogel	
Soft polymer	
Hydrocolloid	
Foam	
Basic wound contact (absorbent dressing/low adherence dressing)	
Film	
Other antimicrobial dressing (please state)	
Other (please state)	

Site ID: | | Date (DD/MM/YY): | | | / | | | / | | Participant ID No: | | | |

AVURT: Form B
Changes to dressing or bandages CONTINUED page 2 of 2

Week number: | |

Date of completion
Day Month Year
| | | | | | |

2. What type of bandage is now being used as the primary bandage? Select one in the table below

If no bandage, please state 'no bandage' in 'other' box below

New bandage	Select one
Four Layer	
3 layer	
3 layer reduced compression	
Reduced compression	
2 layer hosiery (aiming to deliver high compression)	
Reduced compression hosiery	
Other (please state)	

Signature of nurse filling in form B	
Please print name	
Date (DD/MM/YY)	

Please fax to York Trials Unit on: [redacted]

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

AVURT: Form C
Changes to medication

Week number: ☐	Date of completion Day ☐☐ Month ☐☐ Year ☐☐

Please complete giving details of ALL CHANGES to patient's medication

Name of medication			
Reason for taking/change			
Dose		Frequency	
Start date		End date	

Name of medication			
Reason for taking/change			
Dose		Frequency	
Start date		End date	

Name of medication			
Reason for taking/change			
Dose		Frequency	
Start date		End date	

Name of medication			
Reason for taking/change			
Dose		Frequency	
Start date		End date	

Site ID: | | Date (DD/MM/YY): | | | / | | | / | | | Participant ID No: | | | |

AVURT: Form C
Changes to medication CONTINUED

Week number:	

Date of completion		
Day	Month	Year

Signature of nurse filling in form C	
Please print name	
Date (DD/MM/YY)	

Please pass to the named doctor as detailed on the study delegation log to confirm that the patient is still eligible for participation in AVURT

To be completed by named doctor to determine eligibility

	Yes	No*
Following assessment of the changes to medication – is the participant eligible to continue their participation in the AVURT Trial		
***If no please specify reasons**		

***Please confirm the participant has been informed to stop taking their AVURT medication** ☐

***Please ensure a change to Study status form (Form F) is completed**

Signature of doctor assessor	
Please print name	
Date (DD/MM/YY)	

Please fax to York Trials Unit on: [redacted]

Site ID: | | Date (DD/MM/YY): | | / | | / | | Participant ID No: | | | |

AVURT: Form C
Changes to medication
Supplementary page _____(page number)

Week number:		Date of completion Day Month Year 					

Please complete giving details of ALL CHANGES to patient's medication

Name of medication			
Reason for taking/change			
Dose		Frequency	
Start date		End date	

Name of medication			
Reason for taking/change			
Dose		Frequency	
Start date		End date	

Name of medication			
Reason for taking/change			
Dose		Frequency	
Start date		End date	

Name of medication			
Reason for taking/change			
Dose		Frequency	
Start date		End date	

Please fax to York Trials Unit on: [redacted]

AVURT Data Collection File Form C
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Page 1 of 1

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

AVURT: Form D
Reference ulcer healing check/confirmation

Week number: ☐

Date of completion
Day Month Year
☐☐ ☐☐ ☐☐

To be completed two weeks after initial assessment of healing as recorded in the participant data collection file

Please record the following information

1. **Is the reference ulcer healed? Yes*** ☐ **No**** ☐

*If **YES**, Please inform the participant today to stop taking the AVURT medication immediately and arrange for the remaining trial medication to be returned to St George's Research Pharmacy.

*1a Has the participant been informed to stop taking the trial medication?

Yes ☐ **No** ☐

*1b Arrange a date and time to call participant for telephone assessment in week 25 of the study [*Note this will not be required if this form is being completed in weeks 25-27*]

If **NO, the participant will continue in the trial and you should continue to record patient data in the participant data weekly collection file

2a. Please confirm a photograph of the reference ulcer/wound site has been taken ☐

2b. Please confirm a tracing of the reference ulcer has been made ☐

Signature of nurse filling in form D	
Please print name	
Date (DD/MM/YY)	

Please fax to York Trials Unit on: [redacted]

AVURT Data Collection File Form D
Version 1.0 23.04.15
Page 1 of 1

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

AVURT: Form E
Recurrence assessment*

Week number: ☐	Date of completion Day Month Year ☐☐ ☐☐ ☐☐

***To be completed for all participants in week 25 if their reference ulcer healed in week 24 or earlier in the trial (nurse to phone participant to collect data) or if a participant's ulcer recurs.**

1. Is there any new ulcer on the reference leg **Yes**** ☐ **No** ☐

****If YES date of recurrence** Day ☐☐ Month ☐☐ Year ☐☐

2. Please indicate how notification was received ***Please tick one box below***

2a. Nurse phoned participant in 'week 25'	
2b. Participant telephoned clinic to advise ulcer has broken down	
2c. Participant seen in clinic and ulcer/wound site clinically assessed	
2d. Other	

	Yes	No
3. Has the participant experienced any adverse events since last data collection point?		
3a. If yes, was this a serious adverse event (SAE)?		

If YES to any of these questions, please follow the Adverse Event SOP as detailed in the site file
All Adverse Events whether serious or not will be recorded in the clinic notes in the first instance. A record must also be kept in the Sponsor's AE Log JREOLOG0007. SAEs must be notified to the sponsor immediately when the investigator becomes aware of the event (within 24 hours). Refer to JREOSOP0006 and ensure the completed SAE report form JREODOC0012 is sent to the sponsor via fax on [redacted] or E-mailed to [redacted]. If patients stop taking IMP due to an AE or SAE please complete Form F

Signature of nurse filling in form E	
Please print name	
Date (DD/MM/YY)	

Please fax to York Trials Unit on: [redacted]

Site ID: ☐☐ Date (DD/MM/YY) ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

AVURT: Form F
Change to study status page 1 of 2

Week number: ☐	Date of completion Day ☐☐ Month ☐☐ Year ☐☐

Please complete this form when there is a change in the status of a participant

Reasons for change in patient follow-up: *(Place a cross in the appropriate box)*

- ☐ **Participant is being withdrawn from treatment and agrees to further follow up**
- ☐ **Participant is being fully withdrawn from the study**
- ☐ **Participant is lost to follow up**
- ☐ **Participant is being withdrawn from the study and has asked for their data not to be used.**

Reason(s) for withdrawal etc (if known)

Site ID: ☐☐ Date (DD/MM/YY): ☐☐ / ☐☐ / ☐☐ Participant ID No: ☐☐☐

AVURT: Form F

Change to study status CONTINUED page 2 of 2

Week number: ☐

Date of completion
Day ☐☐ Month ☐☐ Year ☐☐

☐ **Participant has died**

A Serious Adverse Event form has been completed Yes ☐ No ☐

Date of death Day ☐☐ Month ☐☐ Year ☐☐

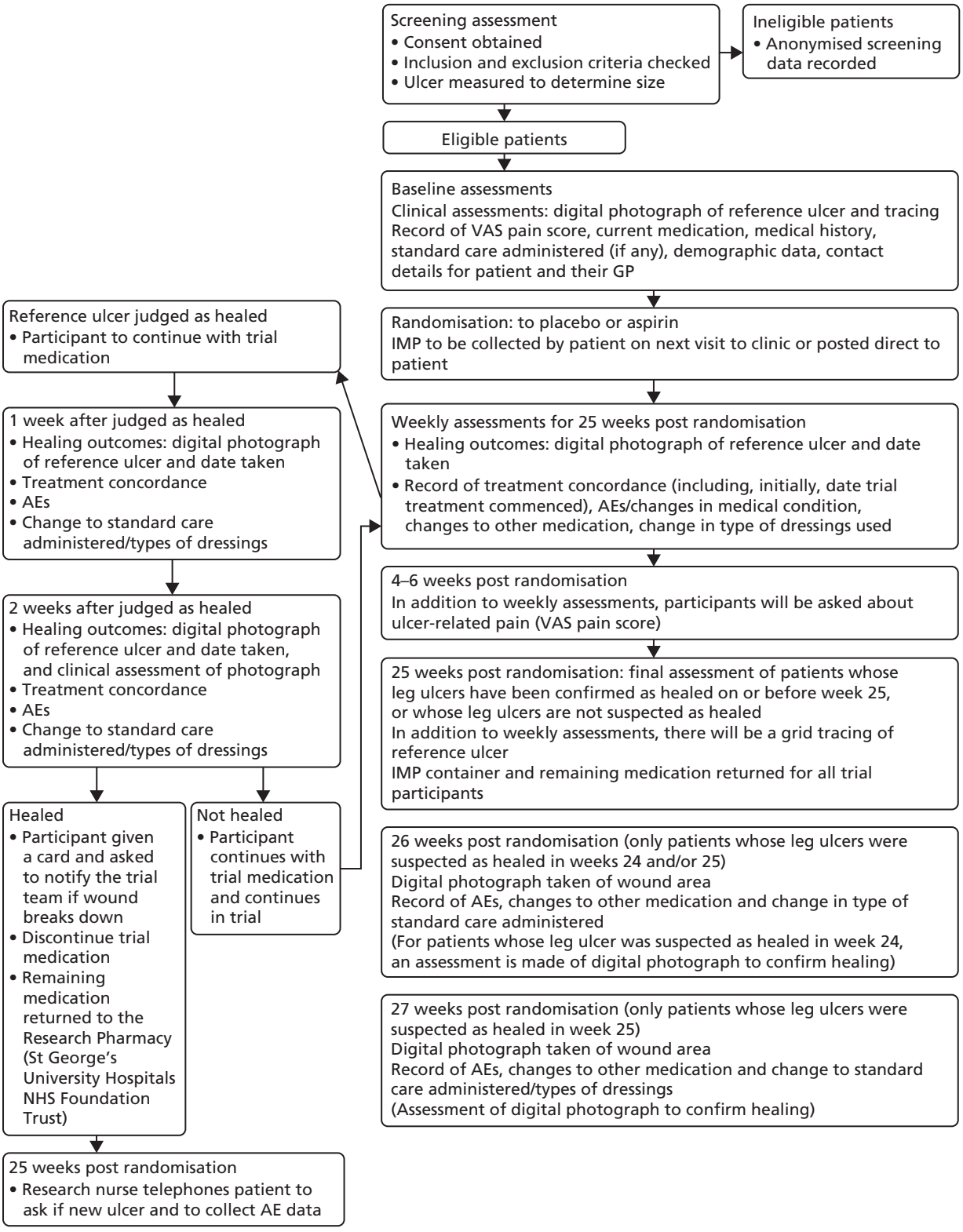
Signature of nurse filling in form F	
Please print name	
Date (DD/MM/YY)	

Confirmed by lead PI/medic	
Please print name	
Date (DD/MM/YY)	

Please fax to York Trials Unit on: [redacted]

AVURT Data Collection File Form F
Version 1.0 23.04.15
Page 2 of 2

Appendix 11 The AVURT flow chart



Appendix 12 Ulcer recurrence card

Version with instructions for site file:

AVURT Trial: 14.0096

Participant Trial ID ☐☐☐ Site ID ☐☐

Date your participation in the study ends:

_____/_____/_____

(Above information to be completed by nurse when card is given to patient)

A NEW ULCER

If you get a new ulcer before the date written date written above your LEFT/RIGHT [NURSE TO DELETE AS APPROPRIATE] leg, please inform your treating clinic as soon as you can:

Name: [Nurse to insert name of contact at the clinic]

At: [Nurse to insert name of clinic]

Contact No: [Nurse to insert phone number for clinic]

V1.0 12/05/2015

Version for printing:

AVURT Trial: 14.0096

Participant Trial ID ☐☐☐ Site ID ☐☐

Date your participation in the study ends:

_____/_____/_____

A NEW ULCER

If you get a new ulcer before the date written above on your LEFT/RIGHT leg, please inform your treating clinic as soon as you can:

Name: _____

At: _____

Contact No: _____

V1.0 12/05/2015

Appendix 13 Study amendments

Ethics submissions

Amendment 1. Substantial (1). Approval not required.

Amendment 2. Substantial (2) and non-substantial (1). Approved 7 May 2016.

Amendment 3. Non-substantial (2). Approved 4 August 2015.

Amendment 4. Substantial (3). Approval not required.

Amendment 5. Substantial (4). Withdrawn.

Amendment 6. Non-substantial (3). Approved 25 July 2016.

Medicines and Healthcare products Regulatory Agency submissions

Amendment 1. Substantial (1). Approved 8 May 2016.

Amendment 2. Substantial (2) and non-substantial (1). Approval not required.

Amendment 3. Non-substantial (2). Approval not required.

Amendment 4. Substantial (3). Approved 14 December 2015.

Amendment 5. Substantial (4). Approval not required.

Amendment 6. Non-substantial (3). Approval not required.

Non-substantial amendments

Amendment 2: non-substantial (1) was not protocol amendment (protocol version 1.3)

Key changes

Minor changes to correct typographical errors and to make clarifications in protocol – sections: 2. Roles and Responsibilities, 3. Study Synopsis, 6.1 Study disease, 7.1 Overall design, 8.1 IMPs and non-IMPs used in the trial, 10. Subject/Patient Recruitment process, 11.1 Informed Consent, 12.1 Screening assessments, 12.2 Treatment procedure, 12.3 Subsequent assessments, 12.5.1 Obtaining, labelling, storing, 12.6.1 Obtaining, labelling, storing, 12.7.1 Obtaining, labelling, storing, 14.3 Data handling and analysis, 16.4.1 Summary of baseline data and flow of participants and appendix 3 Study Flow Chart and Table of Study Assessments.

Informed consent form amended to facilitate five-digit screening ID (ICF1.2).

Amendment 3: non-substantial (2) was a protocol amendment (protocol 1.4)

Key changes

Clarification of management of patients experiencing AEs/SAEs. Protocol amended to state that patients who develop SAEs (and not AEs) to aspirin (or placebo) will be withdrawn from study treatments.

Changes to sections 2. Roles and Responsibilities, 3. Study Synopsis, 6.2 Investigational Medicinal Product (IMP), 6.5 Assessment & management of potential risk, 8. IMP Dosage regimen and rationale, 11.3 Prescribing & Dispensing IMP, 11.6 Discontinuation/withdrawal of participants and stopping rules and 12.1 Screening assessments.

Amendment 6: non-substantial (3) was a protocol amendment (protocol 1.5)

Section 5. Statement to include that unpublished as well as published studies would be included in meta-analysis.

Substantial amendments

Amendment 1: substantial amendment 1 (Medicines and Healthcare products Regulatory Agency) was not a protocol amendment

Simplified IMP Dossier (v2) required adjustment to IMP capsule target weight range.

Amendment 2: substantial amendment 2 (ethics) dated was not a protocol amendment

Two new recruiting sites (Dundee and Lanarkshire) and a change of principal investigator in Bradford.

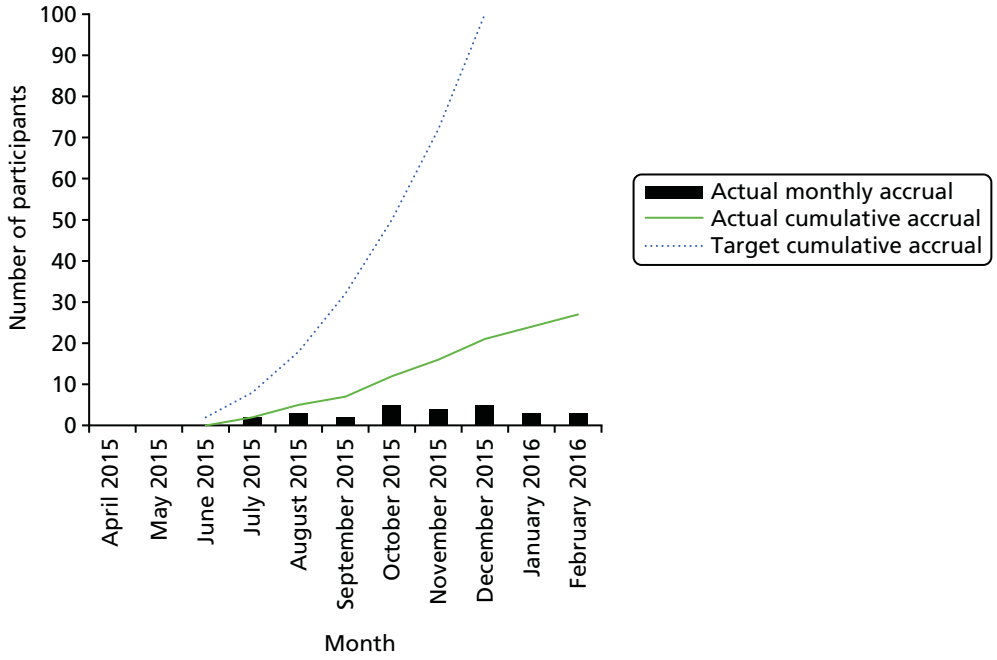
Amendment 4: substantial amendment 3 (Medicines and Healthcare products Regulatory Agency) was not a protocol amendment

Change to the expiry date of the IMP following stability information from Sharp Clinical Services (UK) Limited.

Amendment 5: substantial amendment 4 (ethics) was not a protocol amendment

Change to principal investigator at Wakefield site. Application withdrawn as trial recruitment was stopped.

Appendix 14 Accumulative recruitment over time



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