CLINICAL STUDY PROTOCOL

Aspirin for Venous Ulcers: AVURT

Sponsor's Project Number: 14:0096
EudraCT number: 2014-003979-39
Publicly available Trial Registration Number ID: NCT02333123

Protocol Version and Date. V1.5 27.06.2016

CHIEF INVESTIGATOR (CI):

Mr Robert Hinchliffe
Reader in Vascular Sciences and Honorary Consultant in Vascular Surgery
St George's Vascular Institute
St George's Hospital, Blackshaw Road, London, SW17 0QT

Phone: 07733205706
Email: robhinchliffe@gmail.com

SPONSOR: St George's University of London

SPONSOR REPRESENTATIVE:

Debbie Rolfe
St George's Joint Research and Enterprise Office (JREO)
Hunter Wing, Ground Floor
Cranmer Terrace
London SW17 0RE

Phone: 020 8725 5013 **Email:** drolfe@sgul.ac.uk
Fax: 020 8725 0794

Funding source: NHS National Institute for Health Research Health Technology Assessment Programme (NIHR HTA). NHS support costs from Networks, NHS treatments costs.

Signature Page and Statement

The Chief Investigator (CI) and the Sponsor representative have discussed this protocol version. The investigators agree to perform the investigations and to abide by this protocol except in the case of medical emergency (Section 13.6) or where departures from the protocol are mutually agreed in writing.

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (1998), the St George's NHS Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005' 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

This protocol has been written in accordance to the Sponsor's procedure identified as: JREOSOP0039 'Protocol Design' and is intended for use at UK sites only.

Chief Investigator Mr Robert Hinchliffe Reader and Honorary Consultant in Vascular Surgery St George's, University of London	Signature 	Date 14/07/2016
Sponsor Representative Debbie Rolfe Head of Research Governance St George's University of London	Signature 	Date 14/07/2016

Acknowledgements and Protocol contributories

Mr Robert Hinchliffe (St George's University of London) conceived the study; Professor David Torgerson, Catriona McDaid, Helen Tilbrook (University of York), Debs Rolfe (St George's University of London). Jo Dumville (University of Manchester) helped with trial design. Professor Martin Bland, Dr Rhian Ghabe and Hannah Buckley (University of York) provided statistical expertise. All authors contributed to refinement of the study protocol and approved the final manuscript.

This trial has been awarded funding by the National Institute of Health Research Health Technology Assessment panel to support Research related costs. The Chief Investigator will prepare reports and publications in accordance with the AVURT contract.

Contents

1. List of abbreviations

ABPI	Ankle-brachial pressure index
ACCEPT	Acceptance checklist for clinical effectiveness pilot trials
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CSV	Comma separated values
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
HTA	Health Technology Assessment
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ITT	Intention to treat
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
mmHg	Millimetres of Mercury
MoU	Memorandum of Understanding
NHS R&D	National Health Service Research & Development
NIHR	National Institute for Health Research
NIMP	Non- Investigational Medicinal Product
NSAIDs	Non-steroidal anti-inflammatory drugs
PAD	Peripheral arterial disease
PI	Principal Investigator
PIC	Patient Identification Centre
PIS	Participant Information Sheet
PO OD	Orally, once daily
RCT	Randomised Control Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Document Verification
SIGN	Scottish Inter-Collegiate Guidelines Network
SiMPD	Simplified Investigational Medicinal Product Dossier
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment

SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	Visual Analogue Scale/Score

2. Roles and Responsibilities:

Principal Investigator (PI):

Mr Robert Hinchliffe
St George's Vascular Institute
St George's Hospital
Blackshaw Road
London
SW17 0QT
Phone: 07733205706
Email: robhinchliffe@gmail.com

Senior Trial Statistician:

Dr Rhian Gabe
York Trials Unit, ARRC,
Department of Health Sciences,
The University of York,
Heslington,
York YO10 5DD
E-mail: rhian.gabe@york.ac.uk
Phone: 01904 321399
Fax: 01904 321387

Research Pharmacy:

Nia Al-Samarrai Lead Research Pharmacist
E-mail: Research.pharmacy@stgeorges.nhs.uk
Phone: 020 8725 1294
Fax: 020 8725 4167

Code breaking service

Monday-Friday 9.15am-5.35pm via Research Pharmacy (above)
or via the on-call pharmacist outside of Office opening hours. Contact St George's switchboard 020 8672 1255 and request 'On-Call Pharmacist'

Trial Project Managers

Helen Tilbrook
York Trials Unit
E-mail: helen.tilbrook@york.ac.uk
Phone: 01904 321668
Fax: 01904 321387

Laura Clark
York Trials Unit
E-mail: Laura.clark@york.ac.uk
Phone: 01904 321115
Fax: 01904 321387

Sponsor Representative	Debbie Rolfe St George's Joint Research and Enterprise Office (JREO) Hunter Wing, Ground Floor Cranmer Terrace London SW17 0RE Phone: 020 8725 5013 Email: drolfe@sgul.ac.uk Fax: 020 8725 0794
Clinical Trial Monitor	Arjun Vemula St George's Joint Research and Enterprise Office (JREO) Hunter Wing, Ground Floor Cranmer Terrace London SW17 0RE Phone: 020 8266 6865 (Office) Email: avemula@sgul.ac.uk Fax: 020 8725 0794 Mobile: 07891479588

Trial Management Group:

- Mr Robert Hinchliffe, Chief Investigator
- Professor David Torgerson, Director of York Trials Unit (YTU) will provide methodological advice.
- Dr Catriona McDaid, Senior Research Fellow (YTU) who will support the trial co-ordinators.
- Dr Rhian Gabe, Senior Research Fellow (YTU) senior trial statistician who will support the trial statistician.
- Professor Martin Bland (YTU) medical statistician will provide statistical advice.
- Jo Dumville - health services researcher Chief Investigator of the VenUS IV trial and ran the VenUS II trial.
- Professor Ian Chetter (Hull), Professor Keith Harding (Cardiff), Professor Christine Moffatt (Nottingham), Professor Gerry Stansby (Newcastle) all have experience as either CIs or PIs on large HTA grants in wound healing and particularly leg ulcers. They each run extensive wound healing research programs and are involved in the organisation / delivery of leg ulcer care in their local community.
- Ms Ellie Lindsay, President, Leg Club Foundation.
- Debs Rolfe, Regulatory Assurance Manager & Sponsor representative, St Georges University of London
- Dr Ceri Philips, Chairman of University of Swansea
- Helen Tilbrook & Laura Clark, Trial co-ordinators, YTU, University of York

Trial Steering Committee: Membership: Members of the Committee are listed in the Trial Master File.

Membership will consist of personnel directly involved in the trial and/or independent individuals. The TSC will concentrate on the progress of the trial in relation to protocol compliance and review of any participant safety considerations including the review of any recommendations made by the Data Monitoring Committee if relevant to the trial and to advise the sponsor and/or CI of any decisions.

Data Monitoring Committee: Membership: Members of the Committee are listed in the Trial Master File.

An independent committee established by the sponsor to assess at intervals the progress of the clinical trial, the safety data and the critical efficacy end-points, and to recommend to the Trial Steering Committee whether to continue, modify or stop the trial

3. Study synopsis

Brief Title	AVURT
Official title:	Aspirin for Venous Ulcers: Randomised Trial (AVURT)
Brief Summary	A small randomised, placebo controlled, efficacy study (with potential to extend in to a larger confirmatory study) to examine whether aspirin is effective for venous leg ulcer healing: whether aspirin (at a dose of 300mg) is safe to use in patients with leg ulcers and whether recruitment into a larger study would be possible. We will identify people from community leg ulcer clinics/ hospital outpatients' clinics/Patient Identification Centres (PICs) Consenting patients will be fully assessed in the standard way in a leg ulcer clinic. All patients will receive standard compression bandaging. Patients will be randomised to receive either aspirin 300mg or matching placebo capsules.
Sponsor reference number:	14:0096
Public database Trial identifier number	NCT02333123
Study type & Phase	CTIMP. Phase II
Study Design	A randomised placebo controlled double blind trial
Chief Investigator:	Mr Robert Hinchliffe Reader and Honorary Consultant in Vascular Surgery St George's, University of London
Study Population	Patients presenting to community leg ulcer clinics/hospital outpatients' clinics, or patients registered with leg ulcer clinics but receiving care at home, over a 6 month period with chronic leg ulcers of greater than 6 weeks duration and >1cm^2.
Condition	Venous leg ulcers
Study Group/cohort (s)	Stratification by ulcer size ≤ 5cm^2 or > 5cm^2
Eligibility criteria:	**Inclusion criteria:** ▪ Those with 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. ▪ Ulcer area > 1cm^2

	▪ Participants must have had an ankle brachial pressure index (ABPI) ≥ 0.8 taken within the previous three months or when the ABPI is incompressible other forms of assessment including peripheral pulse examination / toe pressure / duplex ultrasound in combination with clinical judgement to be used to exclude peripheral arterial disease (PAD) ▪ Aged ≥ 18 years (no upper age limit) ▪ Informed consent ▪ Ulcer duration >6 weeks or prior history of venous ulceration
	Exclusion criteria*:* ▪ Unable to provide consent ▪ Unwilling to provide consent ▪ Foot (below the ankle) ulcer ▪ A leg ulcer of non-venous aetiology (i.e. arterial) ▪ Ankle-brachial pressure index (ABPI) <0.8 ▪ Regular concomitant aspirin ▪ Previous intolerance of aspirin/contraindication to aspirin (decision made according to the prescribers' clinical judgement) ▪ Prohibited medication: Probenecid; Oral anticoagulants including coumarins (Warfarin and acenocoumarol) and phenindione; dabigatran; rivaroxaban; apixiban; heparin; clopidogrel; dipyridamole; sulfinpyrazone and iloprost. ▪ Known Lactose intolerance ▪ Pregnancy/lactating / breast feeding women ▪ Male or pre-menopausal female participants of child-bearing potential* unwilling to use an effective method of birth control (either hormonal in the form of the contraceptive pill or barrier method of birth control accompanied by the use of a proprietary spermicidal foam/gel or film ; or agreement of true abstinence (i.e. withdrawal, calendar, ovulation, symptothermal and post ovulation are not acceptable methods) from time consent is signed until 6 weeks after the last dose of IMP ▪ Currently participating in another study evaluating leg ulcer therapies. ▪ Another reason that excluded them from participating within this trial (decision made according to the nurses' or prescribers' clinical judgment) ▪ Previously been recruited in to this trial. *Subjects are only considered not of child bearing potential if they are surgically sterile (i.e. they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal.
Target number of participants:	100
Criteria for evaluation:	***Primary outcome measure(s):*** Time to healing of the reference ulcer (the largest eligible ulcer). Healing will be defined as complete epithelial cover in the absence

	of a scab (eschar) with no dressing required. (Confirmed two weeks in accordance with FDA guidelines - 2006).
	Secondary outcome measure(s): Ulcer size (area) Adverse events Pain score Treatment compliance (Capsule count at the end of the study treatment period and nurse assessment of compression concordance) Resource use
	Other outcome measures if applicable To test the feasibility of study procedures such as recruitment and retention.
Sources of funding:	NHS National Institute for Health Research Health Technology Assessment Programme (NIHR HTA). NHS support costs from Networks, NHS treatments costs.
Anticipated start date:	1 January 2015
Anticipated primary completion date:	30 June 2016
Sponsor	St George's University of London
Contact names	Debbie Rolfe (Sponsor representative) Joint Research & Enterprise Office St George's University of London Tel: 020 8725 5013 Fax:020 8725 0794 Email:drolfe@sgul.ac.uk Mr Robert Hinchliffe Reader and Honorary Consultant in Vascular Surgery St George's, University of London Tel: 07733205706 Email: robhinchcliffe@gmail.com

4. Primary Objectives

The primary objective is to assess the effects of 300mg of aspirin (daily) on the time to healing of the reference ulcer (the largest eligible venous leg ulcer). A two-week period needs to pass from when a wound is first judged as healed until a wound can be confirmed as healed. The first time point will be taken as 'time to healing'.

For patients whose reference ulcer is not suspected as healed or whose reference ulcer has healed, the last follow-up point will be 25 weeks post-randomisation

For patients whose reference ulcer is judged as healed in week 25, the last follow-up point at which healing will be assessed will be two weeks later, 27 weeks post-randomisation.

5. Secondary Objectives

To assess the feasibility of leading directly from the pilot phase II trial into a larger pragmatic study (Phase III) of effectiveness and efficiency conditional on a formal review by the Trial Steering Committee including an independent statistician that would check in accordance with the Acceptance Checklist for Clinical Effectiveness Pilot Trials (ACCEPT Criteria) (Charlesworth, 2013) whether the pilot study fulfilled four criteria:

a) Confirming that the effect sizes in the British and Spanish RCTs (Layton AM, 1994 and del Río Solá, 2012) study were too large; but
b) Confirming that smaller effect sizes were still plausible; while
c) Confirming that the intervention does not lead to unacceptably high rates of serious adverse events; and
d) Confirming that we can recruit at the planned rate.

We will also convene a health professional, researcher and patient group which would determine the minimal clinically important difference (MCID) in time to ulcer healing that might be acceptable to power a larger pragmatic (phase III) trial.

Additional objective

With the data from this study and where data is accessible from other studies, we intend to perform a meta-analysis using the data from other relevant published and unpublished studies.

6. Background

6.1 Study disease

Chronic venous leg ulcers are wounds of the lower limb caused by a diseased venous system which result in chronically swollen legs and damage to the tissues around the ankles. They are most commonly the result of severe varicose veins, a previous deep vein thrombosis or failure of the calf muscle pump. The ulcers may take many months to heal (and some do not) during which time they result in significant suffering for patients and represent substantial cost to the NHS. It is estimated that 1% of the adult population suffer from leg ulcers at some point in their life (Callam, 1992).

The mainstay of treatment of leg ulcers is graded compression therapy to squeeze the fluid out of the leg and venous system. This has been shown to be effective in many clinical trials (O'Meara, 2012). However, despite this treatment patients take many months to heal (with median healing

times of approximately 12 weeks in previous trials (Ashby 2013)) 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.

Furthermore, for many patients the compression therapy is uncomfortable (sometimes painful) and inconvenient for everyday life (compression is bulky and dressings have to be changed several times weekly). If other treatments were able to reduce the time to healing then this would be a significant breakthrough.

At present compression is the main treatment for venous ulceration and few additional therapies exist to improve healing. Surgery to treat varicose veins has been shown to prevent recurrence of ulcers once they have healed and an on-going trial is further investigating surgery as a treatment for chronic ulceration (http://www.nets.nihr.ac.uk/projects/hta/11129197) a drug called pentoxifylline also helps but this is not commonly prescribed in the NHS and has common side effects / drug interactions.

The question being addressed here using a phase II randomised study is whether the addition of 300mg of daily aspirin to standard evidence based therapies demonstrates evidence of a reduction in time to healing of chronic venous leg ulceration. Patients who present at community leg ulcer clinics/ hospital outpatients' clinics, or are registered with a leg ulcer clinic but are receiving care at home, will be recruited. Some sites may use Patient Identification Centres (PICs) to identify patients and invite patients, via letter and/or poster, to take part. As well as assessing the effectiveness of aspirin in patients with venous leg ulcers during the proposed study we will establish the feasibility of satisfactory participant recruitment. We will establish whether patients are compliant with their aspirin therapy and monitor adverse events in this patient population.

This research is important because leg ulcers are common, costly and result in significant patient suffering. If a simple drug (aspirin) which is commonly used in many patients were able to reduce the time to healing of venous leg ulcers this would result in a potentially important reduction in resource use and improvement in patients' health related quality of life. Because aspirin is generally safe, cheap, generally well tolerated and widely available the potential impact on this population is large. However, although two randomised trials have been performed on the use of aspirin in the treatment of venous leg ulcers, the quality of these trials was low. And therefore we need more robust evidence to be able to be sure that aspirin is effective. Furthermore, this study offers the opportunity to systematically assess the safety profile of aspirin in this population as well as assessment of the numbers of people with venous leg ulcers currently taking aspirin or other anti-platelet medications and the potential impact on the design and feasibility of any future study.

6.2 Investigational Medicinal Product (IMP)

Participants will be randomly assigned to receive aspirin 300mg or placebo. Participants will be instructed to take ONE capsule ONCE a day with or after food for 24 weeks. The IMP bottle, upon receipt of an AVURT prescription (original copy), will be despatched from Research Pharmacy at St George's directly to the Participant via an address clearly transcribed and provided by the participant or to the community leg ulcer clinic where recommended storage requirements have been assessed by the Sponsor as acceptable. The Research Pharmacy will have a list of clinics where this option for IMP delivery is available.

IMP will be discontinued if the participant's reference ulcer heals as judged by the local PI, or nominated individual as listed in the Delegation Log (or the CI if the aforementioned are unavailable) or, if a participant develops any intolerable adverse events which in the investigators opinion is attributable to the IMP.

Two small trials (Layton 1994, del Río Solá ML 2012) suggested that high dose (300mg) daily aspirin might improve healing of venous leg ulcers in addition to compression. The only available evidence of effect was generated using this dose. Our trial is a small efficacy study that seeks to examine whether aspirin seems to have an effect (or not) on venous leg ulcer healing and whether aspirin (at a dose of 300mg) is safe to use in people with leg ulcers. The funder's (HTA's) brief was for a proof of concept study and we felt that any signal of effect might possibly be lost if we reduced the dose of aspirin to 150mg or 75mg. If we chose to plan a more complex trial, for example varying the dose or using 3 arms (e.g. placebo versus 75mg versus 300mg aspirin) then the costs would increase significantly and if the higher dose did not demonstrate any suggestion of effect it is unlikely that a smaller dose would do so. Furthermore, the use of the highest dose (300mg) of aspirin might be a dose which could overcome some 'aspirin resistance'.

Aspirin resistance is an interesting concept and one that is not universally accepted as being clinically relevant. We have consulted experts in the field (Prof Khalid Naseem, Professor of Cardiovascular Biology and Head of the Centre for Cardiovascular and Metabolic research, Hull York Medical School and Dr David Allsup, Consultant Haematologist and Honorary Senior Lecturer at Hull and East Yorkshire Hospitals NHS Trust with a clinical interest in Acquired and Constitutional Platelet Disorders on anti-platelets / aspirin resistance and have an expert on anti-platelets as a trial applicant (Professor Stansby). One issue is that the mechanism of action for aspirin in healing venous leg ulcers is not understood and may not be related to its effect on thrombosis. A further key difficulty is that there is no universally agreed definition for aspirin resistance. Testing for 'aspirin resistance' would be possible during the trial but processing the samples will increase costs significantly. Further, testing aspirin resistance would be hard to justify given that aspirin is such a cheap intervention and that resistance is not assessed in routine clinical practice in patients with cardiovascular disease who have an indication for aspirin or other anti-platelet medications.

6.3 Other treatments

All patients will receive/be offered an evidence-based standardised approach to the management of their leg ulcers (standard of care) as per SIGN guidance (http://www.sign.ac.uk/pdf/sign120.pdf) with multi-component compression therapy aiming to deliver 40mmHg at the ankle where possible. The type of dressing used will be at the discretion of the healthcare professional managing the patient (but will be documented in the participant treatment log).

6.4 Study Rationale and risk/benefit analysis

Aspirin is a widely used medication for the long-term prevention of cardiovascular events in patients at increased cardiovascular risk. It is also a commonly used analgesic. At present aspirin is not licenced for use in patients with chronic venous leg ulceration. Patients with chronic venous leg ulceration are generally treated with multi-component compression therapy (bandaging) and in some cases require venous surgery. However despite the use of these treatments ulcers are frequently slow to heal incurring significant costs for the NHS and reduced quality of life for patients. SIGN have recommended the use of pentoxifylline to hasten leg ulcer healing although this is not generally used widely in everyday clinical practice.

Two small randomised trials of aspirin have suggested that aspirin may improve venous leg ulcer healing (Layton 1994, del Río Solá, 2012). These trials have been identified by NIHR HTA as to suggest a possible benefit from aspirin therapy in this group of patients. Furthermore they indicated in their funding brief that aspirin was such a cheap and straightforward intervention that may result in a significant benefit to a large population of patients.

In practice, low dose aspirin (defined as up to 325mg daily – a dose higher than proposed in this study - in one meta-analysis) taken for cardiovascular prophylaxis (a different population) is associated with a modest absolute increase in major bleeding; 769 patients (95% CI, 500-1250) need to be treated with aspirin to cause one additional major bleeding episode annually (McQuaid KR. Am J Med. 2006; 119:624-38). In another meta-analysis published in the BMJ authors were unable to demonstrate any evidence that reducing the dose of aspirin or using modified release formulations would reduce the incidence of gastrointestinal haemorrhage in patients using the medication in the long-term (Derry S. BMJ. 2000;321:1183-7).

6.5 Assessment & management of potential risk

Patients who develop serious adverse effects to aspirin (or placebo) will be withdrawn from study treatments (but will continue in the study to enable an intention to treat analysis). There will be a 24 hour emergency code break for health professionals to contact if they need to determine whether patients are receiving aspirin or placebo for onward clinical management. However in practical terms it will be expected that most clinicians will treat participants with adverse events on the assumption that they had been randomised to receive aspirin.

The side effects of aspirin are well known to healthcare professionals and no specific training is judged to be required. These principally include gastrointestinal upset (dyspeptic symptoms or ulceration) and gastrointestinal haemorrhage. (All known side effects are listed in the SmPC for Aspirin). There is no evidence that minimising the dose will reduce these side effects (see above).

This trial is categorised (in accordance with the MHRA risk adaptive approach): as a CTIMP Type B study. The IMP is double blinded and IMP allocation will be performed centrally by Research Pharmacy at St George's University Hospitals NHS Foundation Trust

Other trial specific risks have been identified as the following;-

The majority of participating sites will be nurse led clinics with no medically qualified doctor permanently on site – these sites will be managed by arranging for a medically qualified doctor to complete trial-related activities (as per Delegation of Duties and Responsibilities Log (JREODOC0013) e.g. eligibility, decision to dose and safety reviews pro-rata. The actual prescribing of IMP may also be required to be delegated to this individual.

Some clinics may not have approved facilities to receive and store IMP until the next scheduled participant visit – in these instances the IMP will be despatched directly to an address of the participant's choice from the Research Pharmacy at St Georges, by an approved courier under temperature controlled conditions. - This is intended to maintain the chain of custody.

Assessment of the sites, staff facilities and their training needs and experience may also influence the intensity and nature of monitoring methods to address specific vulnerabilities at specific sites.

Commonly reported adverse events in patients with venous leg ulcers include: vein ablation, cellulitis of ulcerated leg, over granulation of ulcer, venous eczema, leg oedema, skin breaks with superficial bleeding of ulcer site, increase in ulcer size, new spontaneous ulcers developing, ulcer recurrence, swollen leg or foot, blistering, joining up of ulcers, infected follicles, increasingly odorous and sloughy, increased exudate levels, inflamed skin rash on reference leg, colonization-dark in colour and malodorous, increased ulcer pain.

Pregnancy and breast feeding are exclusion criteria for the study (see section 9.2). All participants taking Aspirin/placebo will be advised that they should use barrier contraception Barrier

contraception should be accompanied by topical spermicidal agents such as foam, gel, cream or film.
Abstinence as an alternative to barrier contraception must be 'true' abstinence. Fertility awareness based methods such as calendar, temperature, cervical mucus, ovulation and post-ovulation methods are not considered true abstinence. Withdrawal during intercourse is also not considered true abstinence.

Commonly reported adverse events due to compression therapy include: Bandage or hosiery related pain and/or discomfort; pressure damage on pressure areas (areas of small radius and/or little padding) such as the malleoli, Achilles tendon, or the front of the foot and is indicated by non-blanching erythema; pressure marks and redness of the skin under a compression bandage: appear mainly in the areas of the tibial edge, the ankle joint, the Achilles tendon and the back of the foot; local damage to the peroneus nerve at the level of the fibula head; maceration of the peri-ulcer skin: presents as swollen, white, soggy skin; excoriation of the peri-ulcer skin: the appearance of red, inflamed skin around the ulcer, thought to be due to wound exudate which contains enzymes; and, infection of the peri-ulcer skin or the ulcer itself: presents usually with a combination of any or all of inflammation, pain, odour, heat and purulent discharge.

7. Trial design

7.1 Overall design

This is a phase II randomised double-blind, parallel group, placebo-controlled trial comparing the effect of 300mg aspirin, orally, once daily (PO OD) in addition to standard care on the healing time of venous leg ulcers.

Standard care is defined as the delivery of care, including compression treatments, normally occurring in participating trial sites. All sites follow evidence-based guidelines and aim to deliver multi component compression (40mmgHg at the ankle) where possible – using reduced compression if this high compression is not tolerated. Patients who do not tolerate any compression will also be included.

Aspirin and matched placebo capsules manufactured and prepared by Sharp Clinical Services UK Limited (SCS), will be identical in appearance to ensure blinding. Patients will be randomly allocated 1:1 to either active or placebo treatment by St George's Hospital Research Pharmacy. The randomisation will be stratified according to ulcer size ($\leq 5cm^2$ or $> 5cm^2$). Treatment allocation is double-blind and will not be revealed until the last data entry point.

We aim to recruit 100 patients over 6 months, in centres across England,Wales and Scotland, from community referral centres or hospital out-patient venous leg ulcer clinics or invited by PICs, with chronic venous leg ulcers (> 6 weeks duration or occurring in a person with a previous history of venous ulceration) and area of $>1cm^2$.

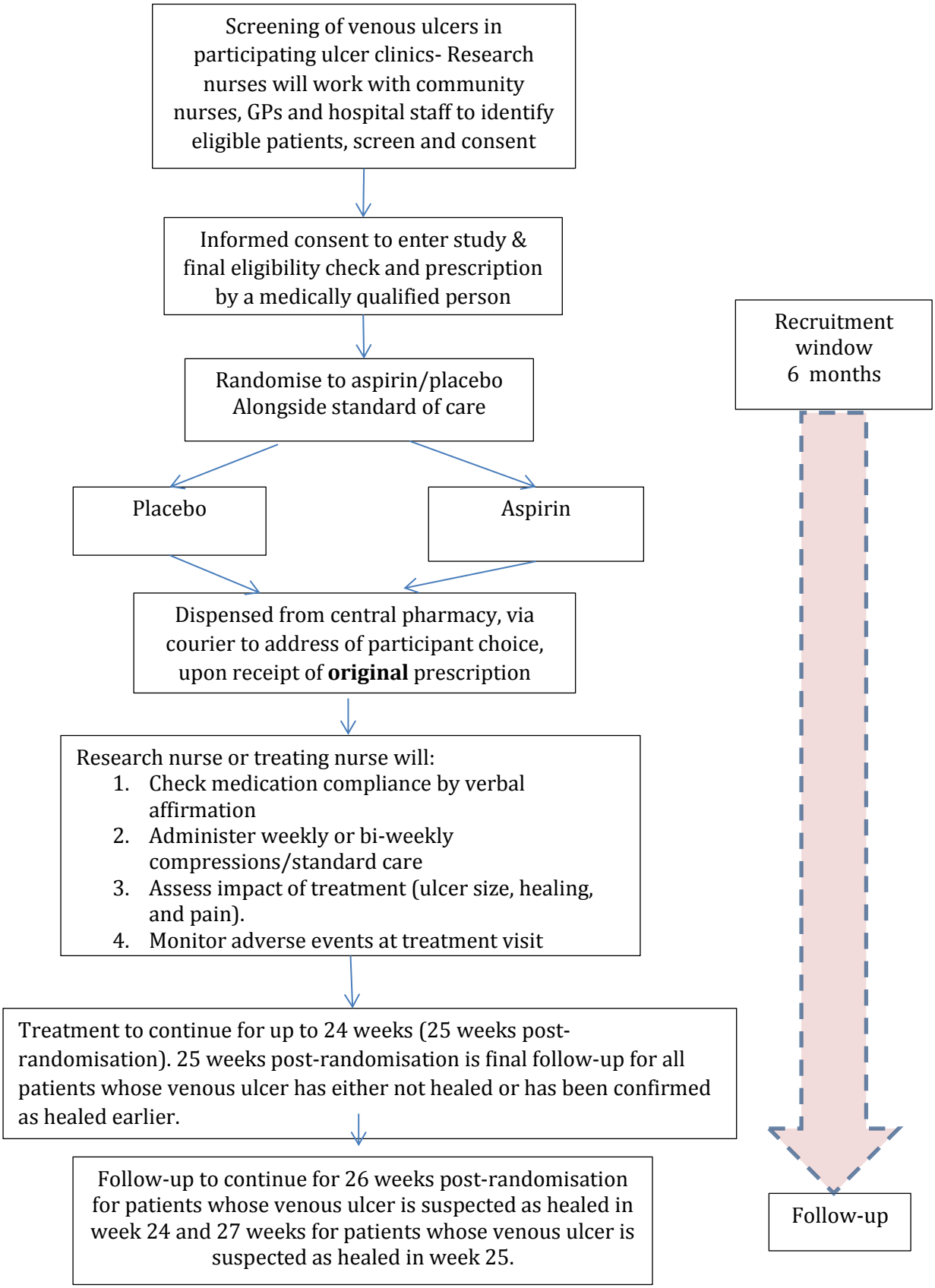
7.2 Treatment period and follow-up

All randomised participants will receive aspirin or placebo for 24 weeks but will instructed to stop taking aspirin/placebo if the leg ulcer has is confirmed healed before then. Following receipt of the AVURT trial medication the participant will be requested to confirm via telephone to the Research

Pharmacy. The Research pharmacy will update the YORK CTU weekly via upload of the AVURT spreadsheet. Participants will be followed up for a minimum of 25 weeks post randomisation.
The primary outcome of this study is time to ulcer healing. Following the ulcer being initially judged to be healed the participant will be followed for a further two weeks to confirm healing in accordance with the FDA guidelines (2006).
Thus participants who have a wound suspected as healed in week 25, will be followed up for two further weeks (26 and 27 weeks post randomisation) to confirm healing.

In the previous HTA Trials on venous ulcers of a similar aetiology to those included here, median time to healing of ulcers was approx. 12 weeks. However the HTA brief was very clear, they wanted a "minimum duration of follow-up of 6 months", and therefore we have adopted this approach.

7.3 Schematic of trial design



8. IMP Dosage regimen and rationale

8.1 IMPs and non-IMPs used in the trial

All participants will be randomised to receive:-

Aspirin 300mg or matched placebo PO OD for 24 weeks

Dosage modifications

Participants will be advised to stop taking aspirin/placebo if
The venous ulcer is confirmed as healed and/or
in the case of either a Serious Adverse Event or an intolerable adverse event which in the investigators opinion could be attributable to the IMP.

Ulcer healing: In cases where the leg ulcer is first judged as healed, a digital photo of the wound area will be taken 2 weeks later. The digital image will be assessed by the PI, (or where unavailable the CI), to determine healing.
If healing is confirmed, the treating nurse or research nurse will advise the participant to stop taking the AVURT medication and return the IMP bottle to the Research Pharmacy via the clinic if a Stamped Address Envelope had not been provided.
If however, the digital image has been assessed and confirmed as 'not healed' the participant will continue to take aspirin/placebo.
At both time-points – first healing judgement and confirmatory ulcer healing – the Trial co-ordinator at York CTU should be informed via fax, phone or via email.

8.2 Source of IMPs including placebo

Aspirin 75mg tablets Intrapharm PL 17509/0024 will be sourced via Research Pharmacy at St George's NHS Healthcare Trust and supplied to Sharp Clinical Services UK Ltd MIA IMP license number 10284

Sharp Clinical Services UK Ltd will over-encapsulate 4 x Aspirin 75mg tablets per capsule. The resulting Aspirin 300mg capsule will appear identical in weight, colour and size to the matched placebo capsules. Placebo capsules will contain a lactose and magnesium stearate blend.

The Aspirin/Placebo capsules will be packaged into child-resistant tamper evident bottles sufficient in size to hold 190 doses for the participant to complete 24 weeks treatment.

The product label will be fully compliant with both Annexe 13 of the Rules and guidance for Pharmaceutical Manufacturers and Distributors (Orange guide) and the protocol

Aspirin/placebo capsules will be stored at ambient room temperature until the expiration/retest date assigned by Sharp Clinical Services UK Ltd

8.3 Accountability procedures for the IMP(s)

The manufactured IMP will be delivered to St George's Research Pharmacy as detailed in the Technical Agreement and will be accompanied by a QP batch release certificate. The IMP will be stored at ambient room temperature in accordance with the specifications on the product label. IMP will be dispensed only in accordance with the protocol and upon receipt of a sponsor approved

AVURT prescription received by the Research Pharmacy Department at St George's. Prescriptions may be faxed ahead to 020 8725 4167 and the original must then be posted "FAO Research Pharmacy, Atkinson Morley Wing, St Georges Hospital, Blackshaw Road, Tooting. SW17 0QT", to allow delivery of the IMP to the participant via their preferred delivery address: home, their work-place or the clinic. Details pertaining to the intended delivery address of the dispensed medication will be detailed on the prescription. If the delivery address indicates a participating clinic the Research Pharmacy will ensure that the clinic has been assessed as meeting the Sponsor requirements for the storage and custody of IMP.

The Pharmacy will be responsible for maintaining an accurate record of the shipment and dispensing of study IMP in the accountability logs. Participants will be requested to telephone Research Pharmacy to confirm receipt of IMP. Research Pharmacy will enter this confirmation into the AVURT spread-sheet for communication to YORK CTU weekly. Participants will be requested to return all IMP containers at the end of their prescribed study period to the Clinical Trial team. The Clinical Trial team at the participating centres will return study participant's IMP to the Research Pharmacy via Stamped Addressed Envelopes provided by York Trials Unit at regular intervals. Upon receipt of returned medication the Research Pharmacy team will complete the accountability log with the capsule count and date of receipt against the participant's dispensed entry.

At the conclusion of the study or upon verification by the sponsor's Clinical Trial Monitor the Participant returned IMP will be entered onto a drug destruction record and the IMP can be destroyed in accordance with the Research Pharmacy IMP destruction procedure.

8.4 Assessment of compliance

Usual nursing staff or the research nurse will regularly ask participants about treatment compliance. Where participants attend clinics, they will be asked to bring the IMP container with them on their visits. The final assessment of compliance will take place at 25 weeks post-randomisation, (at the end of the 24 week course of treatment). Any remaining medication will be returned to the Research Pharmacy in the original IMP bottles to complete the IMP accountability records. Levels of compliance will not influence the decision to continue or stop the trial. Non-compliant participants will continue in the trial and will be followed up and assessed in accordance with the protocol. Reasonable efforts should be made to capture the participants' reasons for non-compliance and notes entered onto their Case Report Forms.

Participants whose leg ulcer is confirmed as healed before week 25 will stop taking the trial medication and the remaining medication will be returned to the Research Pharmacy.

If a participant does not attend the treating clinic or have a home visit at week 25, the research nurse will contact the participant to arrange the return of any remaining AVURT medication.

8.5 Post-trial IMP arrangements

Individual participants will not be provided with further IMP once their study participation ends.

8.6 Name and description of each non-IMP (NIMP)

No NIMPs used.

8.7 Concomitant treatment

Prohibited medication: Probenecid; Oral anticoagulants including coumarins (Warfarin and acenocoumarol) and phenindione; dabigatran; rivaroxaban; apixiban; heparin; clopidogrel; dipyridamole; sulfinpyrazone and iloprost

Combinations that require caution : Other Non-steroidal anti-inflammatory drugs (NSAIDs); ibuprofen; sulphonylureas; digoxin; lithium; diuretics; antihypertensives; acetazolamide; systemic corticosteroids; ciclosporin; tacrolimus; valproate; phenytoin; and Methotrexate used at doses >15mg/week.

8.8 Trial Treatments

All trial participants will be offered an evidence-based standardised approach to the management of their leg ulcers ('standard of care') as per SIGN guidance with multi- component compression aiming to deliver 40mmHg at the ankle where possible. We will not specify a particular compression system or type of dressing used but will leave this to the discretion of the healthcare professional managing the patient (but will record this).

9. Participant Selection criteria

There will be no exceptions (waivers) to eligibility criteria prior to participant inclusion into the study. Any questions raised about eligibility should be addressed prior to entering the participant.

The eligibility criteria have been carefully considered and are standards used to ensure both the safety of the participants and that the trial results can be appropriately used to make future treatment decisions for other people with similar disease or medical condition. It is therefore vital exceptions are not made to the following detailed selection criteria. Deviations from the eligibility criteria are considered to be protocol violation and may be reportable to the MHRA as a serious breach.

All participants that are screened for inclusion into the study must be entered onto the sponsor screening log JREOLOG0001 and will be assigned a sequential number. Participants will be considered eligible for enrolment into this trial if they fulfil all of the inclusion criteria and none of the exclusion criteria as defined below.

Eligible participants will be entered onto the sponsors Subject ID log JREOLOG0002 and assigned a Trial specific Identification number in a pre-agreed format in accordance with Site identifier and next sequential numerical value e.g. SG001

9.1 Inclusion criteria

- Those with 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 etiology 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.
- Ulcer area > 1cm^2
- Participants must have had an ankle brachial pressure index (ABPI) ≥ 0.8 taken within the previous three months. When the ABPI is incompressible other forms of assessment

including peripheral pulse examination / toe pressure / duplex ultrasound in combination with clinical judgement to be used to exclude PAD
- Aged ≥ 18 years (no upper age limit)
- Informed consent
- Ulcer duration > 6 weeks or prior history of venous ulceration

9.2 Exclusion criteria

- Unable to provide consent
- Unwilling to provide consent
- Foot (below the ankle) ulcer
- A leg ulcer of non-venous aetiology (i.e. arterial)
- Ankle-brachial pressure index (ABPI) <0.8
- Regular concomitant aspirin
- Previous intolerance of aspirin/contraindication to aspirin (decision made according to the prescribers' clinical judgement)
- Prohibited medication: Oral anticoagulants including coumarins (warfarin & acenocoumarol) and phenindione, dabigatran, rivaroxaban and apixaban (the last three are the current 3 NOACs that are licenced), heparin, clopidogrel, dipyridamole, probenecid, sulfinpyrazone & iloprost
- Known lactose intolerance.
- Pregnancy/lactating or breast feeding women
- Male participants or pre-menopausal female participants of child-bearing potential * unwilling to use an effective method of birth control (either hormonal in the form of the contraceptive pill or barrier method of birth control accompanied by the use of a proprietary spermicidal foam/gel or film ; or agreement of true abstinence (i.e. withdrawal, calendar, ovulation, symptothermal and post ovulation are not acceptable methods) from time consent is signed until 6 weeks after the last dose of IMP
- Currently participating in another study evaluating leg ulcer therapies.
- Another reason that excluded them from participating within this trial (decision made according to the nurses' or prescribers' clinical judgement)* *
- Previously been recruited in to this trial.

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

**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

10 Subject/Patient Recruitment process

Participant recruitment at a site will only commence once evidence of the following are in place:

1. REC approval and Clinical Trial Authorisation (CTA)
2. Signed Delegation of Duties Sponsorship Agreement (JREODOC0013) returned to the JREO
3. Final sponsorship (which will include evidence of Pharmacy Green light) issued by the sponsor representative of the JREO
4. Host site approval issued by JREO,
5. The trial initiation procedure completed and the issue of the 'Open to recruitment' letter by the JREO

All sites participating in the trial will also be asked to provide a copy of the following:

1. Signed Clinical Trial Site Agreement (CTSA),
2. Host site (R&D approval)

Treating staff or a research nurse considered to be part of the local care team at each centre will receive training on the AVURT trial protocol. They will screen patients on their current caseloads in addition to new patients to identify potential participants. Where measurements such as the ABPI are not available these will be undertaken as part of standard clinical care.

Potential participants will be provided with both verbal and written information (AVURT patient information leaflet) in a face–to–face meeting with the research team member. Patients invited by PICs will also receive written information in advance of a face-to-face meeting. A minimum of 24 hours to consider participation in the trial should be given. In cases where a patient provides consent at their next appointment at the clinic, the initial screening check will be reviewed to determine if the patient's medication or medical condition has changed.

Every effort will be made by the recruiting clinics to access details of medications already prescribed to potential participants via GP patient medical summaries. Patients may be asked to also bring all of their prescribed medications to their next visit to clinic in order to ensure eligibility.

In all cases, a medic will determine a patient's eligibility. Consent will be obtained prior to review by the medic and the patient informed that their eligibility would be subject to confirmation by a medic. If the potential participant is not known to the clinic medic, the participant may be contacted via phone to check for any possible contra-indications.

If a potential participant is assessed as not eligible for study entry they will be informed and thanked for any effort and time given thus far.

Venous ulceration will be confirmed by clinical criteria (as per VENUS I Trial). (See appendix 2)

11 Study Procedures

11.1 Informed consent

Please note, it is essential that all trial personnel/staff undertaking the informed consent process has signed the Sponsor's Delegation of Responsibilities Log JREOLOG0004 to ensure that the person has been delegated the responsibility by the study CI/PI. All personnel taking informed consent must be GCP trained. Refer to Sponsor SOP JREOSOP0027

Informed consent from the participant or legally authorised representative must be obtained following explanation of the aims, methods, benefits and potential hazards of the trial and before any trial specific procedures are performed. The only procedures that may be performed in advance of written informed consent being taken are those that would have been performed on all participants in the same situation as routine clinical practice.

Written informed consent can be obtained up to two weeks after the patient was first approached and given information about the trial, prior to randomisation. Consent will be taken during the patient's visit to the clinic or a home visit by a member of the research team as per Delegation log.

The Investigator or designee will explain that the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

Consent will comprise a dated signature from the patient and the signature of the person who obtained informed consent.

Patients giving informed consent will be randomised and entered in to the trial. Baseline clinical and demographic data will be collected by the nurse (as per Delegation of Responsibilities log JREOLOG0004) and the patient will be asked to complete a visual analogue (VAS) pain score (Appendix 4)

In order to ascertain recruitment rates and aspects of generalisability, an anonymised Screening log JREOLOG0001 will be kept of all patients who present with venous ulceration to the community clinics / hospital out-patient venous leg ulcer clinics or who are registered with a clinic but receive treatment at home. These will be used to collect information on the reason for non-randomisation. Recruitment sites using PICs will be asked to report number of patients invited to participate.

Those unable to speak or read English will have access to a NHS interpreter as per standard clinical practice. For recruiting centres in Wales: if a patient requests translation of documents in to Welsh the necessary arrangements will be made. We are aware of the requirements of the Welsh Language Act (1993) and will work locally with the NISCHR Permissions Co-ordinating Unit (PCU) to translate the documents if required. However, English is the first language for the majority of the population in the recruitment area in Wales.

A copy of the signed Informed Consent Form (ICF) along with a copy of the most recent approved Patient Information Sheet (PIS) will be given to the study participant. An original signed & dated consent form will be retained in the medical notes, and a copy will be placed in the ISF.

A letter informing the participant's GP they have consented to the study will be faxed or posted to their GP's surgery.

If new safety information results in significant changes to the risk–benefit assessment, the consent form will be reviewed and updated if necessary. All participants, including those already being treated, will be informed of the new information, given a copy of the revised consent form and asked to re-consent if they choose to continue in the study.

11.2 Randomisation procedure

One randomisation list will be produced in advance by the IMP manufacturer Sharp Clinical Services UK Ltd and will be provided to Research Pharmacy at St George's Hospital. Half the randomisation list will mirror the other half and will include randomisation numbers/IMP container allocations. Where the participant is added to the randomisation list (top or bottom) will depend upon the stratification – (participant ulcer size ≤ 5cm^2 or > 5cm^2 added) which will be clearly indicated on the individual AVURT prescription

The IMP container labels will include a unique container ID corresponding to the randomisation list. All participants will be given a study specific 24hrs emergency contact card immediately after the prescription is signed and forwarded onto the Research Pharmacy. The card includes details of the study: Study title, details of IMP(s), patient trial number, CI/PI's contact details along with out of hours contact details in case of emergency.

Upon receipt of the randomisation list produced by Sharp Clinical Services UK Ltd. a copy will be provided to the senior trial statistician at York Trials Unit.

11.3 Prescribing & Dispensing of IMP

The sponsor Research pharmacy will construct a protocol specific Clinical Trial Procedure which will detail participant management in relation to IMP dosing and pharmacy dispensing procedures. The research pharmacy will also provide a study specific prescription template to be used for the study.

All IMP prescriptions presented to pharmacy must be on the Sponsor pharmacy approved template and be signed and dated by an approved AVURT prescriber. The prescriber must have been signed off by the PI on the Staff delegation of duties log JREOLOG0004 for that task. A sample signature of all delegated prescribers must be provided for the Research Pharmacy Site File prior to receipt of the 1st trial prescription. Upon site initiation completed delegation logs will be copied by the Sponsor Clinical Trials Monitor and filed in the Research Pharmacy Site File held at St Georges. Prescriptions received at St George's by a non-approved prescriber will not be acceptable and will cause the participant unnecessary delays

All AVURT IMP will be dispensed centrally by the Research Pharmacy at St George's Hospital. Upon receipt of a valid prescription the Research Pharmacy staff will assign the next available pack number as indicated on the randomisation list. The allocation will be in accordance with the ulcer size as indicated on the prescription. If the ulcer size ≤ 5cm^2 the participant will be allocated the next available ascending number – if the ulcer size > 5cm^2 then the participant will be allocated the next available number from the bottom of the randomisation list.

The prescription must clearly state the name of the participant, the participant trial ID, the trial centre ID, the ulcer size ≤ 5cm^2 or > 5cm^2 and the desired delivery destination that the dispensed IMP should be delivered to.

St George's Pharmacy will include in the package: - a 24 hour emergency contact card; a request for the participant to confirm receipt of the IMP via phone to the Research Pharmacy and the dispensed IMP.

St George's Pharmacy will send the package to the agreed delivery destination (as indicated on the prescription) by temperature controlled courier upon receipt of the original signed prescription. Centres will be encouraged to commence aspirin/placebo in participants as soon as possible after randomisation, this might be at the participant's next visit to the clinic (where an approved clinic delivery address was indicated) or sooner where the IMP was delivered directly to the participant.

The participants will be encouraged to telephone Research Pharmacy to confirm receipt of IMP (where receipt of IMP is not via the clinic). The Research Pharmacy staff will add the date of confirmation to a spreadsheet which will be shared with York CTU on a weekly basis when recruitment activity is evident. The spreadsheet will also contain information such as participant screening ID, site ID, actual date of randomisation and study ID allocated at IMP randomisation.

11.4 Emergency unblinding

Research Pharmacy at St George's will hold the code-break envelopes which will contain the treatment allocation for each unique IMP container ID. Research Pharmacy will provide 24 hour cover for emergency code breaks via the on-call pharmacist outside of normal office hours in accordance with the Research Pharmacy code break procedure CTP SOP A11. The contact details will be included on the IMP bottle and will also be included on the 24 hour emergency contact card provided to the participant.

A copy of the treatment allocation lists will be held by the senior trial statistician at the York Trials Unit for the purpose of interim data analysis for the DMC and final analysis. The list will be confidential to the trial statistician and interim reports will be summarised as treatment arm A and B, and not by Aspirin and placebo.

11.5 Overdose of Trial medication

Single doses <100mg/kg are unlikely to cause poisoning

Common features of salicylate poisoning include vomiting, dehydration, tinnitus, vertigo, deafness, and sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Some degree of acid-base disturbance is present in most cases. A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH is usual. Acidosis may increase salicylate transfer across the blood brain barrier.

Uncommon features of poisoning include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopaenia, increased INR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema.

Central nervous system features including confusion, disorientation, coma and convulsions are less common in adults.

Treatment

Give activated charcoal if an adult presents within one hour of ingestion of more than 250mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features should be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by administration of 1.26% sodium bicarbonate.

The urine pH should be monitored. Correct metabolic acidosis with intravenous sodium bicarbonate 8.4% (1st check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema. Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations > 700mg/L (5.1mmol/L) or lower concentrations associated with severe clinical or metabolic features. Patients > 70 years have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

11.6 Discontinuation/withdrawal of participants and stopping rules

In consenting to the trial, participants are consenting to trial treatments, trial follow up and data collection. However, an individual participant may stop treatment early or be stopped early for any one of the following reasons:

- Unacceptable treatment toxicity which in the investigators opinion is attributable to the IMP or a Seriousadverse event
- Intercurrent illness that prevents further protocol treatment
- Any change in participant's condition that is in the investigator's opinion justifies the discontinuation of treatment
- If participants become pregnant or suspect a pregnancy during the trial we will retain them in the trial for follow-up purposes, but they would be advised to stop taking their aspirin/placebo immediately.
- Withdrawal of consent from the participant
- Reference ulcer confirmed as healed

As participation in the trial is entirely voluntary, the participant may choose to discontinue treatment at any time without penalties or loss of benefits to which they may be entitled. Although not obliged to give a reason for discontinuing their trial treatment/ protocol inclusion a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights. Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow up (except in cases where consent is withdrawn), and data analysis.

If a participant chooses to discontinue they should be continued to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. However if the participant confirms they do not wish to participate in the scheduled follow up data collection visits then data that has already been collected should be kept and analysed according to the ITT principle for all participants who stop follow up early.

Participants who stop the trial follow up early will not be replaced.

11.7 Participant transfers

If a participant moves from the area making continued follow up at their consenting centre inappropriate, every effort should be made for them to be followed up at another sponsor approved trial centre. Written consent should be taken at the new centre and then a copy of the participant's CRF should be provided to the new centre. Responsibility for the participant remains with the original consenting centre until the new consent process is complete.

11.8 Lost to Follow up

Reasonable efforts should be made to minimise participants lost to follow up. However it would be acceptable to consider a participant as 'lost to follow up' if there has been no response to at least 2 separate attempts to reach the participant by telephone by either the clinical or research staff and 1 attempt by letter by research staff over the course of 4 weeks.

11.9 Definition of the End of Trial

This is defined as the Last Patient Last Visit (LPLV) completing their 6 month follow-up assessment.

The REC and the MHRA requires notification of the end of trial within 90 days of its planned completion or within 15 days if the study is terminated early. Refer to JREOSOP0015 and inform the JREO to facilitate assistance and compliance with requirements

12 Study Assessments

12.1 Screening assessments

- Clinical assessment: Tracing of largest eligible ulcer (or Grid or ruler placed near ulcer) to determine if ulcer size is greater than > 1cm^2
- Chronic venous leg ulcers (> 6 weeks duration or occurring in a person with a previous history of venous ulceration).
- Record actual duration of largest ulcer (the reference ulcer) or prior history of venous ulceration.
- In line with previous NIHR HTA (VenUS I & IV) trials of patients with venous ulceration, a pragmatic clinical diagnosis (with confirmation of an ABPI ≥ 0.8 to exclude peripheral arterial disease) of venous ulceration will be sufficient to identify potential research participants. No additional tests (including duplex ultrasound scanning or angiography) will be required. Patients will be screened for a previous diagnosis of Aspirin contraindications and will be excluded at the discretion of the recruiting nurses' or prescribers' clinical judgement.

Following consent: confirmation of eligibility criteria: refer to section 9

Baseline assessments (after consent and before randomisation)

a. Clinical assessment: Digital photograph of the largest eligible ulcer to record size of ulcer for baseline assessment.
b. Clinical assessment: Tracing of largest eligible ulcer (or grid or ruler placed near ulcer) to determine ulcer size (for randomisation).
c. Ulcers on both legs to be drawn on a leg diagram with the largest eligible ulcer (the reference ulcer) to be clearly labelled.
d. Duration of largest eligible ulcer.
e. Record of Ankle Brachial Pressure Index (ABPI) measurement of reference leg and date taken.
f. Level of mobility (e.g. walking, partially mobile, immobile).
g. Diabetes (Type I or II)
h. Body Mass Index (BMI)
i. Demographic data: Gender, sex, smoking status.
j. Participant will be asked about ulcer related pain over previous 24 hours: Visual analogue (VAS) pain score (Appendix 4).
k. Participant's contact details (name, address, telephone numbers and email address) and GP details (name of GP, name of surgery and address).
l. Compression bandaging administered and measure of compression aimed for.
m. Total number of ulcer episodes on reference leg including reference ulcer.

12.2 Treatment procedure

All eligible participants will be prescribed Aspirin 300mg or placebo capsules PO OD for 24 weeks by an authorised prescriber. The authorised prescriber will have been delegated the prescribing function by the PI. The completed delegation log will have been faxed ahead to the Research Pharmacy at St George's University Hospitals NHS Foundation Trust on fax number 020 8725 4167. The completed prescription will be faxed to the Research pharmacy to facilitate treatment allocation. The original prescription will need to be posted to Research Pharmacy to facilitate despatch of the dispensed IMP.

All trial participants will be offered an evidence-based standardised approach to the management of their leg ulcers ('standard of care') as per SIGN guidance with multi- component compression aiming to deliver 40mmHg at the ankle where possible. We will not specify a particular compression system but instead will list those systems deemed to fit this criterion). Patients will be eligible even if they are unable to tolerate compression or use reduced compression. We will not be specific about the type of dressing used and leave this to the discretion of the healthcare professional managing the patient (but will record this).

12.3 Subsequent assessments

Participants will not be asked to attend any additional visits for research purposes. The participants will be seen in their regular clinical environment or during regular home visits by their treating nurse and/or a research nurse. Participants are routinely seen in clinic or have home visits by their nurse at least twice a week to start and then usually once a week as the ulcer improves (weekly digital photo is typical) - and most are followed-up regularly for signs of deterioration even if healed.

The additional study related activities for each participant will be:-

a. Taking Aspirin or placebo PO OD
b. Provision of data and a pain score at baseline and 4, - 6 weeks post-randomisation (approximately 4-6 weeks post 1st dose of IMP).
c. Provide information about adverse event occurrence & affirmation of continued use of effective contraception.
d. IMP compliance checks via verbal affirmation at each visit and capsule count at end of IMP treatment performed by Research pharmacy, St George's.
e. Keep a diary of changes to any concomitant medication and/or bring in prescription copies or prescribed medication on a regular basis.
f. Phone Research Pharmacy to advise receipt of trial medication (if sent to participant's home address).
g. If ulcer heals before the end of the study, participant to phone to advise if a new ulcer occurs on reference leg before the end of study.

<u>Weekly assessments for 25 weeks post-randomisation</u>

If patients are seen every two weeks rather than every week for routine treatment for their leg-ulcer(s), then the trial assessments will be conducted every two weeks and not weekly. If a patient is not seen for routine treatment for a period of three weeks, the research nurse, or nominated individual as listed on the delegation log, will phone patient to collect assessments.

<u>Assessments:</u>

- Healing outcomes
- Treatment concordance (IMP compliance and compression bandaging)
- Adverse events/side effects/change in health status
- Change to concomitant medication

<u>Resource use:</u>

- Number of visits, types of dressings used and level of compression aimed for.

Healing outcomes will be assessed weekly by the treating or research nurse. A digital photograph will be taken of the reference ulcer weekly. The digital photos will include the date that the image was taken. If a digital photo cannot be taken, a grid tracing of reference ulcer will be made.

Once healing is suspected the treating nurse or research nurse will contact the Trial Co-ordinator at York Trials Unit via fax, phone or email to advise the date that healing is suspected. The PI, or nominated individual as listed in the Delegation Log, or the CI, will evaluate the digital image of the ulcer area to determine healing. A week later another photo will be taken of the wound area and 2 weeks from the date of suspected healing a further assessment and photo will be taken. The participant will continue to take the aspirin/placebo during this 2-week period. The exception will be for patients whose leg ulcer healed at week 25; they will not take medication during these 2 weeks as the course of medication should be complete. At the second assessment, the PI, or nominated individual named on the Delegation Log or the CI, will evaluate the second digital image of the ulcer area to determine healing. If healing is confirmed, the treating nurse or research nurse will advise patient to stop taking aspirin/placebo. The nurse will contact the Trial co-ordinator at York Trials Unit via fax, phone or email to confirm whether the ulcer has healed or not.

If the wound has remained healed then the first date will be taken as the point of healing. The patient will be given a card with the contact details of the research nurse, or nominated individual as listed on the delegation log, and their end date in the study (i.e. 25 weeks post-randomisation). The patient will be asked to contact that person if they get a new ulcer on their reference leg ulcer reoccurs before their specified end date in the study. If the wound has broken down in the interim it will not be classed as healed and the participant will carry on in the study until healing is confirmed.

Treatment compliance: Initially patients will be asked to confirm the date that they started taking the IMP. Subsequently, confirmation of treatment compliance will be by verbal affirmation from the participant. The nurse will not be equipped to conduct an actual capsule count at each visit. If applicable, the nurse will also try to obtain reasons for any non-compliance with treatment.

Adverse events: The treating or research nurse will ask about any possible adverse events/side effects. If any are reported then these will be recorded and reported in accordance with SOP ID JREOSOP0006

Concomitant medication: The treating or research nurse will ask about any changes to concomitant medication.

Resource use: The treating or research nurse will complete a treatment log. They will initially record the type of dressing administered and level of compression aimed for and will subsequently only record a change in the type of dressing administered and level of compression. The number of times the participant visits the clinic and/or had a home visit will also be recorded.

<u>5 weeks post-randomisation (approx. 4 weeks post 1st dose of IMP)</u>

<u>Assessments</u>:

- Weekly assessments
- Ulcer related pain over last 24 hours (VAS Pain score)
- Time of day trial medication is taken

In addition to the weekly assessments and resource use data described above, the treating nurse, research nurse or nominated individual as listed in the Delegation Log, will see patients at five weeks post-randomisation to ask participants about ulcer related pain over the last 24 hours and complete a Visual Analogue Scale (VAS) and the time of day that the trial medication is taken. Outcomes will be entered onto a hard copy Case Report Forms (CRFs).

If a patient's leg ulcer has healed before this time point, the treating nurse, research nurse, or nominated individual as listed in the Delegation Log, will phone the patient for their pain score and any adverse events.

25 weeks post-randomisation

Assessments:

- Weekly assessments
- Ulcer recurrence

IMP:

- Container and remaining medication returned.

In addition to the weekly assessments and resource use data, at 25 weeks the treating nurse or research nurse will assess healing by measuring the size of the reference ulcer, which will be determined by a digital photograph and a grid tracing. If the participant heals, the treating nurse or research nurse will confirm with a second digital photograph 2 weeks later (at 27 weeks). The assessment at 25 weeks post-randomisation will be the last assessment of participants whose leg ulcer has not healed.

The research nurse, or delegated individual, will phone participants whose leg ulcer healed before 25 weeks, and who therefore no longer attend the clinic, to ask if the reference ulcer has reoccurred and collect data on adverse events.

The IMP container will be collected by the treating or research nurse and returned to the Research Pharmacy at St Georges Hospital to facilitate a capsule count and compliance reconciliation.

26 weeks post-randomisation

Assessments:

- Healing outcomes – Digital photo
- Adverse events/side effects/change in health status
- Change to concomitant medication

Resource use:

- Change in type of dressings used and level of compression aimed for.

Only patients whose leg ulcer is suspected of healing at 24 and 25 weeks post-randomisation will be assessed at 26 weeks. At 26 weeks post randomisation the treating nurse or research nurse will take a digital photo of the wound area.

Usual nursing staff or research staff will also ask about changes to other medication and any possible adverse events/side effects. If any are reported then these will be recorded and reported in accordance with SOP ID JREOSOP0006

If there is a change to the type of dressing administered this will be recorded in the treatment log.

27 weeks post-randomisation

Assessments:

- Healing outcomes – Digital photo
- Adverse events/side effects
- Change to concomitant medication

Resource use:

- Change in type of dressings used and level of compression aimed for.

Only patients whose leg ulcer is suspected of healing at 25 weeks post-randomisation will be assessed at 27 weeks. At 27 weeks post randomisation the treating nurse or research nurse will take a digital photo of the wound area.

Usual nursing staff will also ask about changes to other medication and any possible adverse events/side effects. If any are reported then these will be recorded and reported in accordance with SOP ID JREOSOP0006

If there is a change to the type of dressing administered this will be recorded in the treatment log.

12.4 Summary flow chart of study assessments

Refer to Appendix 3

12.5 Digital Photos of Leg Ulcers and Tracings

The main outcome assessment will be collected by anonymised, (identified only by the participant's unique id), digital photos of leg ulcers which will be stored in the York Trials Unit (YTU).

12.5.1 Obtaining, labelling, storing

a. Nurses will take digital photos of the participants' reference leg ulcers. To ensure accuracy in assessing the size of the ulcer a scale/ruler will be placed alongside the ulcer in the photo. The ruler/scale should also show the participant's unique id and date so that these are also displayed in the photo. Photos will be transferred to the YTU via the University of York's hosted electronic DropOff Service, where files are temporarily stored on a University of York Server on campus until they are retrieved by the YTU and stored on their secure sever. The photos will be anonymised and encrypted by the site before uploading them to the DropOff Service. The nurses should not delete the photos from their cameras until they have received confirmation from the YTU that they can do so. If a site is unable to upload the photos, then the memory card containing the anonymised photos should be securely posted to the YTU or the YTU will make arrangements for the photos to be collected. The anonymised digital photos should be uploaded to the DropOff service, or posted to the YTU, as soon as possible after the clinic.

b. Leg ulcer tracings will be anonymised, (identified only by the participant's unique id), and kept on the patient's file. The ulcer size should be recorded on the CRF.

12.6 Case Report Forms (CRFs) and Treatment Logs

Other outcomes and assessment will be collected on hard copy case report forms (CRFs) and treatment logs.

12.6.1 Obtaining, labelling, storing

a. CRFs and treatment log data will normally be collected during a participant's visit to clinic or by a treating nurse or research nurse during a home visit. In some cases the data will be collected over the phone. The CRFs and logs will include the patient's unique id and the date the assessment was made. They will not include the patient's name.

b. Original CRFs and logs will be stored on the Investigators' site files.

c. Anonymised copy CRFs and treatment logs will be faxed by nursing or research staff to the YTU fax number: 01904 321387. Teleform software or manual entry will be used to record the CRF data into a Microsoft SQL Server 2008 R2 database. The same version of SQL will also be used for the Management and Survey databases. Data for analysis will be extracted as comma separated values (CSV) files.

d. Hard copies of CRFs, and treatment logs will be stored in the YTU, which will be manually entered and also stored electronically

12.7 Date of healing

Date of healing will be collected by the Trial Co-ordinator at York CTU and recorded in the participant's CRF

12.7.1 Obtaining, labelling storing

a. The treating nurse or research nurse will fax, phone or email the Trial Co-ordinator at York CTU with the date that wound is judged to be healed, confirmed as healed or confirmed as broken down. The nurse will supply the date and the participant's unique ID. The Trial Co-ordinator at York CTU will enter the data into a secure online management database.

13 Pharmacovigilance

13.1 Definitions

Adverse Event (AE)—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 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 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 (AR)—any untoward and unintended responses to an IMP related to any dose administered.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)—any Adverse Event or Reaction that at any dose:

- Results in death; or

- Is life-threatening (places the subject, in the view of the Investigator, at immediate risk of death)
- 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, for a pre-existing condition)
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions)
- Consists of a congenital anomaly or birth defect (in offspring of subjects or their parents taking the IMP regardless of time of diagnosis).
- Or is 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 the definition of serious will also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR) — An Adverse Reaction which is classed in nature as both serious and unexpected.

An 'Unexpected Adverse Reaction' is when both the nature and severity of the event is not consistent with the reference safety information available for the IMP in question.

13.2 Investigator responsibilities relating to safety reporting

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 participant's CRF and the Sponsor's AE Log JREOLOG0007.

SAEs and SARs must be notified to the sponsor immediately 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 020 8725 0794 or E-mailed to adverseevents@sgul.ac.uk.

Two way communications will be utilised between the Sponsor Representative and the Trial Co-ordinator at York CTU York Trials Unit to ensure both organisations are in possession of the same safety information.

The sponsor will notify all SUSARs to the MHRA electronically and the REC utilising the eSUSAR system.

The sponsor will inform the MHRA and the REC of fatal or life threatening SUSARs as soon as possible, but no later than 7 calendar days after the receipt of the SAE report form. Any additional information will be reported within 8 days of sending the initial report.

The sponsor must report all other SUSARs and safety issues to the MHRA and REC, as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting.

Causality Assessment—must be made by a medically qualified doctor as these decisions require medical and scientific judgment as well as knowledge of the participant concerned. The investigator must assess the causality of all SAEs or SARs in relation to the IMP using the following descriptions:

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 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 is used the sponsor will assume the event is related to the IMP until follow up information is received from the investigator to confirm a definitive causality assessment

Any SUSAR assessed as related to the IMP will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

Expectedness should be based solely on the available RSI for the IMP and will be described using following categories:

Expected—an AE that is classed in nature as serious and which is consistent with the information about the IMP listed in the RSI or clearly defined in this protocol.

Unexpected—an AE that is classed in nature as serious and which is not consistent with the information about the IMP listed in the RSI

The completed AE Log JREOLOG0007 will be sent to Sponsor upon request and/or every 2 months.

The Chief or Principal Investigator will respond to any SAE queries raised by the Sponsor as soon as possible. Follow up reports must continually be completed within acceptable time-frames and sent to the sponsor as detailed above until the reportable event is considered resolved.

13.3 Notification of deaths

Only deaths that are assessed to be caused by the IMP will be reported to the Sponsor. This report will be immediate or within 24 hours of first knowledge.

13.4 Development Safety Update Reports (DSURs)

The CI or a delegated PI will prepare the DSUR, using the Sponsor's template and in accordance with the Sponsor's DSUR SOP JREOSOP0008. It will be reviewed by the Sponsor and when necessary be referred to an independent committee (i.e. Research Governance Safety Committee). The sponsor will provide the REC and the MHRA with the prepared DSUR at least annually and within the defined reporting timelines.

13.5 Annual Progress Reports (APRs)

The Chief Investigator will prepare the APR in accordance with JREOSOP0043. Following review by the sponsor the report will be sent to the REC. The APR is due for submission annually within 30 days of the anniversary date on which the favourable opinion was given by the Ethics committee, until the trial is declared ended.

13.6 Reporting Urgent Safety Measures

The sponsor and Investigator may take appropriate urgent safety measures in order to protect the participants against any immediate hazard to their health or safety. If such measures are taken the sponsor shall immediately or no later than 3 days from the date the measures are taken give written notice to the MHRA and REC of the measures taken and the circumstances given rise to such measures. The CI must notify the sponsor immediately to facilitate compliance with the regulations.

Refer to sponsor SOP Management of Amendments JREOSOP0011 for guidance

13.7 Notification of Serious Breaches of GCP and/or the protocol

Any Protocol Deviations, Violations will be documented using JREODOC0061, and entered onto the sponsor's log JREOLOG0005. Potential Serious Breaches and Urgent Safety Measures will be recorded both on the Sponsor's Log JREOLOG0005 and processed according to JREOSOP0012 and where necessary JREOSOP0032

A "serious breach" is a breach which is likely to effect to a significant degree:

(a) The safety or physical or mental integrity of the participants of the trial; or
(b) The scientific value of the trial.

The CI will notify the Sponsor immediately of any case where there exists a possible occurrence of a serious breach

14 Data management and quality assurance

14.1 Confidentiality

All data will be handled in accordance with the Data Protection Act 1998.

The Case Report Forms (CRFs) will not bear the participant's name or other directly identifiable data. The participant's trial Identification Number (ID) only, will be used for identification. The sponsor Subject ID log JREOLOG0002 can be used to cross reference participant's identifiable information.

14.2 Data collection tool

Digital cameras will be purchased for the study.

Case Report Forms (CRFs) including treatment logs will be designed by the CI and York Trials Unit and the final version will be approved by the Sponsor. All data will be entered legibly in black ink with a ball-point pen. If the Investigator makes an error, it will be crossed through with a single line in such a way to ensure that the original entry can still be read. The correct entry will then be clearly inserted. The amendment will be initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid will not be permitted.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The Staff Delegation of Responsibilities Log JREOLOG0004 will identify all trial personnel responsible for data collection, entry, handling and managing the database.

All protocol-required information collected during the study must be entered by treating staff or the research nurse (or individual named in the Delegation Log), in the case report form. Details of case report form completion and correction will be explained to the staff responsible for completing the forms. The designated representative should complete the case report form during the patient's visit to clinic or home visit. An explanation should be given for all missing data.

A source data location list will be prepared prior to the start of the study. This list will be filed in both the trial master file and the investigator study file and updated as necessary. All clinically relevant data must be recorded in the patient notes (source), in addition to a statement that all trial relevant data is recorded in the CRF.

The completed case report form must be reviewed and signed by the principal investigator or by a designated individual.

CRFs will be completed by treating staff or the research nurse (or individual named in the Delegation Log) by asking the patient questions. Data on non-trial medications will obtained by: asking the patient; a diary of medications completed by the patient; reviewing medical notes; and, reviewing the patients' prescriptions or prescription medications presented at study visits. Data on medical conditions will be obtained by asking the patient and reviewing medical notes.

Anonymised CRFs should be faxed to the YTU within a week of completion.

14.2 Incidental findings

Normal referral procedures would be followed in the scenario that an incidental finding was suspected.

14.3 Data handling and analysis

There will be two main databases used in the management of trial data. The database management system will be used to record trial activity such as adding new participants, updating participant status, and managing receipt of Case Report Forms (CRFs) etc. The survey data will be held in a separate database, and the processing of this data is supported by two temporary databases. All CRFs will be manually entered and verified using Teleform software by data entry personnel. Data will then be downloaded into an SQL database and the data checked against the faxed hard copy of the CRF. Each process will be documented; initialled and dated on the Scanning Log Sheet. The YTU Data Manager will write a Validation Plan for the CRFs in consultation with the trial co-ordinator and trial statistician. The Plan will include detail coding for the CRFs and data query resolution rules/procedures. One of the rules included in the plan is, that a log will be kept at the YTU detailing any changes made to entries in the CRFs. The log will be sent to sites for them to amend accordingly their copy of the CRF. A copy of the log will be sent to the trial monitor to facilitate chasing up and resolution. The Validation Plan will be agreed by the trial statistician and Sponsor.

All YTU data recorded electronically will be held in a secure environment with permissions for access as detailed in the delegation log. Teleform Software (Version 10.7) will be used to design the CRFs. Teleform Software is a commercial off the shelf software used by the YTU data management team for many years.

Quality Control should be applied at each stage of data handling to ensure that all data are reliable and have been processed correctly.

15 Archiving arrangements

The trial essential documents along with the trial database will be archived in accordance with the sponsor SOP JREOSOP0016. The agreed archiving period for this trial will be defined within the Delegation of Duties Sponsorship Agreement JREODOC0013

Each PI at any participating site will archive the trial essential documents generated at the site for the agreed archiving period in accordance with the signed Clinical Trial Site agreement

16 Statistical design

16.1 Statistical input in trial design

Professor Martin Bland and Dr Rhian Gabe are providing senior statistical oversight of the trial. They have reviewed and contributed to the protocol. Contact details are given in the roles and responsibilities section (Section 2).

16.2 Endpoints

Time to healing and reduction in ulcer size are being used as key signals of effectiveness. If there is no evidence for an enhanced time to healing *or* favourable changes in ulcer size favouring the aspirin group, there would be insufficient evidence to proceed to a larger trial.

Digital photographs of the ulcers will be taken from each patient on a weekly basis until healing has occurred or the participant exits the trial – we will use specialist software to calculate wound area from these pictures.

16.2.1 Primary endpoints

The primary outcome measure will be time to healing of the reference ulcer (the largest eligible ulcer). This will take the form of survival time data for analysis.

For patients who are observed to have healed, time to healing will be measured in days from date of randomisation until the first date healing has been recorded. Healing will be defined as complete epithelial cover in the absence of a scab (eschar) with no dressing required.

In most patients who do not heal, we expect the last date they are assessed for wound healing to be approximately 25 weeks from randomisation as this represents the end of planned follow up. However, some patients could have been lost to follow up, withdrawn, or died. For patients in whom healing has not been recorded, time from date of randomisation until patients exit the trial, withdraw, are lost to follow up or die will be used in the survival analysis, whichever occurs first.

16.2.1.1 Secondary endpoints

- Ulcer size (area) measured in cm^2 by specialist software
- Recurrence of reference ulcer
- Adverse events
- Ulcer related pain using the VAS Score
- Treatment compliance (capsule counting and nurse assessment of compression concordance)
- Resource use: Number of visits to clinic and/or home visits and types of dressings used.

16.3 Sample size and recruitment

16.3.1 Sample size calculation

The current study is a phase II randomised trial aiming to recruit 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 (del Rio Sola 2012, Layton 1994).

The primary outcome of AVURT is 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, 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 (Ashby 2013). Applying this to a smaller sample of 100, implies the standard error of such a sample would be increased to 0.22 (obtained from 0.105 x $\sqrt{}$(448/100)). A 95% confidence interval for the log hazard ratio would thus be the estimate of the log (HR) ± 1.96×0.222 = log(HR) ± 0.435. The antilog of this is 1.54 and the 95% confidence interval for the hazard ratio would be the observed value divided or multiplied by this. Hence if our hazard ratio were the same as that suggested by the existing studies, i.e. about 1.5, our confidence interval would be (0.97, 2.31) which just includes 1.00.. It would be unlikely that, if the hazard ratio is as these two previous smaller studies suggest, we would observe an overall hazard ratio below 1.00. To further increase the power of the comparison we will undertake a meta-analysis with the previous Spanish study (del Río Solá, 2012). Compliance and follow-up will be measured as part of the study and so there is no formal inflation of the recruitment target for drop-out.

An important secondary outcome is wound area and whether it would be possible to detect changes that might be as a result of treatment with aspirin. Using data from the Venus I study of compression bandaging (Iglesias 2004) we analysed measured ulcer areas for 245 participants who were measured within 60 days of recruitment. Ulcer area has a highly skewed distribution, so we calculated difference detectable in log area at follow-up, after adjustment for log ulcer area at baseline and time elapsed until follow-up. The residual standard deviation 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 will have multiple measurements of wound area and so should be able to detect smaller differences.

16.3.2 Planned recruitment rate

Previous UK venous leg ulcer RCTs have recruited up to 3-4 patients per centre per month (Ashby 2013, Jull 2008, Nelson 2007). However, given the exclusion of patients already taking aspirin or intolerance to aspirin we conservatively estimate that 1.5 patients will be recruited per centre per month (a local assessment in a trial centre established 30% of patients take aspirin, which is similar to the proportion quoted in the Spanish study by del Río Solá, 2012). We intend to recruit from up to 13 sites in England and Wales.

16.4 Statistical analysis plan

16.4.1 Summary of baseline data and flow of patients

A CONSORT diagram displaying the flow of participants through the trial will be presented (http://www.consort-statement.org/). This will include a breakdown for each trial arm, the number of eligible patients considered for the trial, consenting, randomised, receiving the intended treatment, completing the study protocol, and analysed for the primary outcome.

The proportions of screened potential participants who are ineligible due to aspirin use and who are ineligible for other reasons, the proportions of those eligible who decline, with reasons if known, and who agree to participate will be presented.

Patient characteristics and clinical baselines measurements will be summarised descriptively by trial arm. These measures include ethnicity, age, BMI, sex, smoking status, diagnosis of diabetes by Type I or II , area and duration of the reference ulcer, left/right reference leg, total ulcers on reference leg, patient's level of mobility, Ankle brachial pressure index of reference. No formal statistical comparisons will be undertaken of baseline factors by trial arm. Continuous measures will be reported as means and standard deviations, or medians with ranges while the categorical data will be reported as counts and percentages.

16.4.2 Primary endpoint analysis

The primary analysis will be conducted in accordance with the principles of intention to treat with all events analysed according to the participant's original, randomised treatment allocation, irrespective of deviation based on non-compliance.

Time to ulcer healing will be presented by trial arm using a Kaplan-Meier plot and a logrank survival comparison will be made. The median time to healing will be presented overall and by trial arm with corresponding 95% CIs. The numbers included in the analysis will be reported by trial arm, as will the numbers of those unhealed and censored due to reaching the end of the study, being lost to follow up, withdrawing, or dying.

The primary analysis will investigate differences in the primary outcome by trial arm using Cox's proportional hazards regression and adjusted by area and duration of the reference ulcer and centre. Area and duration of ulcer will be logarithmically transformed and included as fixed effects. The model will be tested for inclusion of shared centre frailty effects.. Proportional Hazard assumption will be evaluated through inspection of plots and by a statistical test using Schoenfeld residuals.

16.4.3 Secondary endpoint analysis

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

The proportion of patients who are found to have a recurrence of the reference ulcer, within the time-frame of study will be reported by trial arm. Time to recurrence will be investigated in a similar fashion to the primary analyses, i.e. plotting Kaplan-Meier curves, performing a log rank test and estimating HRs with the Cox model adjusted for ulcer area and duration. Ulcers that were suspected as healed but had been confirmed as not healed in the assessment two weeks later would not be classed as an ulcer that had reoccurred.

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

Compliance will be reported in terms of proportion of patients completing the course of treatment up to healing or planned trial exit and compared between arms using a chi-2 test and 95% CIs. The number of pills taken by each patient will also be compared and compliance with the recommended compression will also be presented.

Mean and median pain scores will be presented by treatment arm at each time-point assessed.

16.4.4 Sensitivity and other planned analyses

An individual patient level meta-analysis using the data from the published studies in addition to the data generated from AVURT is planned. However, if this data is not obtainable we will undertake an aggregated meta-analysis of AVURT and the Spanish study (del Río Solá 2012).

16.4.5 Health Economic analysis

An economic analysis will not be conducted.

16.5 Randomisation

The aspirin / placebo manufacturer (Sharp Clinical Services UK LTD) will provide one randomisation list. The randomisation list will be mirrored top to bottom – bottom to top to facilitate participant allocation according to stratification. Where the participant is added to the randomisation list (top or bottom) will depend upon the stratification. Stratification will be performed according to ulcer size (≤ 5cm^2 or > 5cm^2) only as this is the strongest predictor of outcome and the study has a small sample size, making it unsound to have too many factors to stratify.

16.6 Interim analysis

There are no planned interim analyses during the course of this phase II trial. The Trial Management Group (TMG) will monitor recruitment and discuss emerging compliance and safety issues at their meetings as required. The Data Monitoring Committee (DMC) will review overall recruitment, compliance, data-completeness with respect to primary outcome and unblinded overall safety data to determine patterns and trends of events at approximately 4 month intervals, with blinding being maintained through closed sessions. The Trials Steering Committee will meet approximately every 6 months, shortly after the DMC and formally review recruitment, compliance and safety at these time points but blind to allocation, unless requested otherwise in which case a closed session between the independent members of the TSC and the statistician would be held.

16.7 Other statistical considerations

A statistical analysis plan (SAP) will be drafted by the statistician and finalised before unblinding of results. Updates will be managed using version control, dates and a section in at the end of the SAP dedicated to listing changes.

17 Committees involved in the trial

There will a Trial Management Group (TMG), independent Data Monitoring Committee (DMC) and Trial Steering Group (TSC). Terms of reference will be provided for these committees. A full membership list for each committee will be held in the TMF held at York CTU.

The TMG will include the CI, co-applicants (including a statistician), the trial co-ordinator and data manager as detailed at the front of the protocol. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

The TSC will include an independent chair person, a patient representative and others. The Trial Steering Committee should agree the trial protocol and any protocol amendments and provide advice to the Investigators on all aspects of the trial. A Trial Steering Committee may have members who are independent of the Investigators, in particular an independent chairperson. Decisions about continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the Trial Steering Committee

The DMC will review the accruing trial data and assess whether there are any safety issues that should be brought to participants' attention or any reasons for the trial not to continue The Data Monitoring Committee should be independent of both the Investigators and the funder/Sponsor and should be the only body that has access to unblinded data. It will normally make recommendations to the Trial Steering Committee (or Trial Management Group).

18 Direct access to source data

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

19 Site approval and ongoing Regulatory compliance

Before any site can enrol patients into the trial, the Principal Investigator must apply for Host site approval from the Trust Research & Development (R&D) and be granted written NHS R&D approval. Refer to JREOSOP0017 'Obtaining St Georges Healthcare NHS Trust approval' and contact the governance team within the sponsor JREO for any assistance. The site must conduct the trial in compliance with the protocol as agreed by the sponsor and, by the regulatory authority as appropriate and which was given favourable opinion by the Research Ethics Committee (REC).

The Chief Investigator will be provided (via the sponsor) with file indexes i.e. JREODOC0003 TMF index and JREODOC0004 ISF index for use with SOP JREOSOP0019 'Preparation and Maintenance of the TMF' The CI will be responsible for the maintenance of the TMF and will delegate the responsibility of ISF file maintenance to the PI at each participating site.

It is the responsibility of the Principal Investigator at each site to ensure that all subsequent amendments gain the necessary approval. Refer to JREOSOP0011 'Management of Amendments'. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section 13.6 for details of reporting procedures/requirements).

Within 90 days after the end of the trial, the CI and Sponsor will ensure that the REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial. Refer to JREOSOP0015 'End of study declaration'

The CI will supply an End of Study report of the clinical trial to the MHRA and REC within one year after the end of the trial. The sponsor can provide JREODOC0059 End of study Report template

20 Monitoring plan for the trial

The CI will be requested to complete the JREODOC0032 Risk Assessment Questionnaire and forward to the sponsor to facilitate appropriate costing and Sponsorship in Principle to be issued prior to REC application.

The trial will be monitored according to the risk based monitoring plan JREODOC0030 agreed by the Sponsor. The purpose of trial monitoring is to provide oversight during the conduct of the trial to give reassurance that the study protocol and procedures are being followed, that legal/governance requirements are being complied with, and that the critical data collected are reliable.

Triggered visits may occur for poor data return or protocol adherence concerns or unusual frequency of SAEs in comparison to other similar sites.

It is the responsibility of the CI to ensure that the Sponsor's self-monitoring template is completed and submitted as instructed (refer to the Study Monitoring Plan for detail). The JREO governance team will determine the initial project risk assessment and justify change as the study progresses.

The PI at each collaborating site in addition to site monitoring visits may also be required to complete self-monitoring form(s) and must return the form to the sponsor for review and action. Failure for any PI to comply with requests for on behalf of the sponsor may be escalated in accordance with JREOSOP0031 Escalation Procedure; the site may also be selected for a GCP audit.

It is the sponsor's responsibility to ensure that any findings identified in any monitoring report are actioned appropriately and in a timely manner and that any violations of GCP or the protocol will be reported to the CI & sponsor representative. Any serious breach will be handled according to JREOSOP00032 Serious Breach Reporting

Any urgent safety measures at either the CI or a PI site must be reported by that site Investigator within 3 days, as per UK Regulations.

The CI will be provided with a copy of the study monitoring plan during the Trial Initiation monitoring visit.

21 Finance

This study has been awarded an NHS National Institute for Health Research Health Technology Assessment Programme (NIHR HTA) grant to cover the Research related costs. NHS support costs from Networks, NHS treatments costs will be covered through the normal treatment pathway

22 Insurance and indemnity

St George's University of London holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that St George's has been negligent. This includes negligence in the writing of the protocol, or selection of trial resources.

Where the Trial is conducted in a hospital, the hospital has a duty of care to participants. St George's University of London will not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees

and a copy of the relevant insurance policy or summary shall be provided to St George's University of London, upon request.

Participants may be able to claim compensation for injury caused by participation in this Trial without the need to prove negligence on the part of St George's University of London or another party.

If a participant indicates that they wish to make a claim for compensation, this needs to be brought to the attention of St George's University of London immediately.

Failure to alert St George's University of London without delay and to comply with requests for information by the sponsor or any designated Agents may lead to a lack of insurance cover for the incident.

23 IP and development policy

Unless otherwise specified in agreements, the following guidelines shall apply: All Intellectual Property Rights and Know How (IP) related to the Protocol and the Trial are and shall remain the property of the Sponsor excluding

1) pre-existing IP related to clinical procedures of any Hospital.

2) pre-existing IP related to analytical procedures of any external laboratory .

All contributors:

- shall assign their its rights in relation to all Intellectual Property Rights and in all Know How, not excluded above to the Sponsor and at the request and expense of the Sponsor, shall execute all such documents and do all such other acts as the Sponsor may reasonably require in order to vest fully and effectively all such Intellectual Property Rights and Know How in the Sponsor or its nominee.
- shall promptly disclose to the Sponsor any Know How generated pursuant to this Protocol and not excluded above and undertake treat such Know How as confidential information jointly owned between it and the Sponsor

Nothing in this section shall be construed so as to prevent or hinder and medical professional from using Know How gained during the performance of the Trial in the furtherance of its normal business activities, to the extent such use does not result in the disclosure or misuse of Confidential Information or the infringement of any Intellectual Property Right of the Sponsor.

24 Publication policy

Publication: "Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations."

All scientific contributors to the Trial have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives.

To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication prematurely. Lead in any publications arising from the Trial shall lie with the Sponsor in the first instance.

24.1 Before the official completion of the Trial,

All publications during this period are subject to permission by the Sponsor. If an investigator wishes to publish a sub-set of data without permission by the Sponsor during this period, the Funder shall have the final say.

Exempt from this requirement are student theses that can be submitted for confidential evaluation but are subject to embargo for a period not shorter than the anticipated remaining duration of the trial.

24.2 Up to 180 days after the official completion of the Trial

During this period the Chief Investigator shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer-review with a view to publication in a reputable academic journal or similar outlet as the Main Publication.

- The Chief Investigator shall be senior and corresponding author of the Main Publication.
- Insofar as compatible with the policies of the publication outlet and good academic practice, the other Investigators shall be listed in alphabetic order.
- Providers of analytical or technical services shall be acknowledged, but will only be listed as co-authors if their services were provided in a non-routine manner as part of a scientific collaboration.
- Members of the Steering Group shall only be acknowledged as co-authors if they contributed in other capacities as well.
- If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Chief Investigator shall ask the Steering Group to arbitrate.

24.3 Beyond 180 days after the official completion of the Trial

After the Main Publication or after 180 days from Trial end date any Investigator or group of investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee. Sponsor's reasonable comments shall be reflected. All publications related to the Trial shall credit the Chief and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

25 Statement of compliance

The trial will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 1998, the Human Medicines Regulations 2012, the Medicines for Human Use (Clinical Trial) Regulations 2004, and with all relevant guidance relating to medicines and clinical studies from time to time in force including, but not limited to, the ICH GCP, the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the NHS Research Governance Framework for Health and Social Care (Version 2, April 2005).

This study will be conducted in compliance with the protocol approved by the REC and according to GCP standards and UK Clinical Trials Regulation. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and REC except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Sponsor and REC as soon as possible.

26 List of Protocol appendices

Appendix 1 Protocol Amendment/Revision History (chronological order)

Appendix 2 Definition of a Venous Leg Ulcer

Appendix 3 Study Flow Chart & Table of study assessments

Appendix 4 Visual Analogue Scale (VAS)

27 References

Ashby RL, Gabe R, Ali S, Adderley U, Bland JM, Cullum NA, Dumville JC, Iglesias CP, Kang'ombe AR, Soares MO, Stubbs NC, Torgerson DJ. Clinical and cost effectiveness of compression hosiery versus compression bandages in treatment of venous leg ulcers (Venous leg Ulcer Study IV, VenUS IV): a randomised controlled trial. Lancet. 2013 Dec 5. pii: S0140-6736(13)62368-5. doi: 10.1016/S0140-6736(13)62368-5

Callam MJ. Prevalence of chronic leg ulceration and severe chronic venous disease in western countries. Phlebology 1992;7(Suppl 1):6-12.

Charlesworth G, Burnell K, Hoe J, Orrell M, Russell I. Acceptance checklist for clinical effectiveness pilot trials: a systematic approach. BMC Med Res Methodol. 2013 Jun 13;13:7

del Río Solá ML, Antonio J, Fajardo G, Vaquero Puerta C. Influence of aspirin therapy in the ulcer associated with chronic venous insufficiency. Ann Vasc Surg. 2012 Jul;26(5):620-9

Derry S. Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. BMJ. 2000;321:1183-7).

http://www.nets.nihr.ac.uk/projects/hta/11129197

http://www.sign.ac.uk/pdf/sign120.pdf

Iglesias C, Nelson EA, Cullum NA, Torgerson DJ; VenUS Team. VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers. Health Technol Assess. 2004 Jul;8(29):iii, 1-105

Layton AM, Ibbotson SH, Davies JA, Goodfield MJ. Randomised trial of oral aspirin for chronic venous leg ulcers. Lancet. 1994 Jul 16;344(8916):164-5.

McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med. 2006; 119:624-38

O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD000265. DOI:10.1002/14651858.CD000265.pub3

Jull A, Arroll B, Parag V, Waters J. Pentoxifylline for treating venous leg ulcers. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD001733

Nelson EA, Prescott RJ, Harper DR, Gibson B, Brown D, Ruckley CV. A factorial, randomized trial of pentoxifylline or placebo, four-layer or single-layer compression, 3 and knitted viscose or hydrocolloid dressings for venous ulcers. J Vasc Surg. 2007 Jan;45(1):134-41.

FDA US Department of Health and Human Services Food and Drug Administration. Guidance for Industry Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment. June 2006. [Accessed on 11 Nov 2014 http://www.fda.gov/cder/guidance/index.htm]

Appendix 1

Protocol amendment /Revision History

Protocol Version and Date	New text
V1.1 (23/12/2014) Following REC review and feedback (Submitted as a response to REC)	Clinicaltrials.gov : NCT02333123 Section 6.5 text describing risk measures surrounding pregnancy potential and breast feeding Section 9.2 & Study Synopsis exclusion criteria to exclude pre-menopausal women of child-bearing potential and male subjects unwilling to use effective methods of birth control Definition of pre-menopausal women of child bearing potential and acceptable forms of contraception Section 10 Included statement that patients should be given a minimum of 24 hours to consider taking part in trial before consent is taken Section 11.1 Included consideration of translation for welsh patients upon request Section 11.6 Withdrawal of participants that do become pregnant
V1.2 (20/01/2015) Following REC review and feedback (Submitted as a response to REC)	Section 3 Warfarin; coumarin; heparin; phenindione; clopidogrel and dipyridamole listed in the exclusion criteria. Section 8.7 Warfarin; coumarin; heparin; phenindione; clopidogrel and dipyridamole listed under 'prohibited medication' and removed from 'combinations that require caution' Section 9.2 Warfarin; coumarin; heparin; phenindione; clopidogrel and dipyridamole listed in the exclusion criteria.
V1.3 (28TH April 2015)	Section 2 – TMG membership updated, Typographical errors corrected Section 3, 6.1, 7.1, 10 and 11.1 Use of Patient Identification Centre (PIC) added and Scotland added to section 7.1 Section 8.1, 12.3 and 12.7.1 Option of fax to York CTU added Section 11.1 removal of countersignature requirement on ICF

	Section 12.1 Additional question "Total number of ulcer episodes" Section 12.2 incorrect reference to Appendix 4 removed Section 12.3 clarification of ulcer reoccurrence on reference leg. Collection of VAS score can occur between weeks 4-6 to accommodate fortnightly visits. Additional question about time of day IMP medication is taken. Section 12.5.1 processing of leg ulcer tracings and upload of digital photos clarified Section 12.6.1 and 14.3 reference to Teleform amended Section 16.4.1 collection of ethnicity for analysis added Appendix 3 – Schedule of events corrected
V1.4 (Amendment 3) 27th July 2015 To correct protocol erratums & provide clarity with regards to possible adverse event, serious adverse event & patient management	Section 2 – Opening hours of Research Pharmacy 9.15am-5.35pm Section 3 & 11.3 :-Ulcer size should read $\leq 5cm^2$ or $> 5cm^2$ Section 6.2 : IMP will be discontinued if the participant's reference ulcer heals as judged by the local PI, or nominated individual as listed in the Delegation Log (or the CI if the aforementioned are unavailable), or, if a participant develops any aspirin related intolerable adverse events which in the investigators opinion is attributable to the IMP. Section 6.5 : Patients who develop serious adverse effects to aspirin (or placebo) will be withdrawn from study treatments (but will continue in the study to enable an intention to treat analysis). There will be a 24 hour emergency code break for health professionals to contact if they need to determine whether patients are receiving aspirin or placebo for onward clinical management Section 8 : Dosage modifications Participants will be advised to stop taking aspirin/placebo if The venous ulcer is confirmed as healed and/or in the case of either a Serious Adverse Event or an intolerable adverse event which in the investigators opinion could be attributable to the IMP

	Section 11.6 Unacceptable treatment toxicity which in the investigators opinion is attributable to the IMP or a Serious adverse event Section 12.1 4th Bullet point should read :- ABPI ≥ 0.8
V1.5 27 June 2016	Secondary objective amended to include the intended use of unpublished studies as well as published studies.

Appendix 2

Definition of a venous leg ulcer

A venous leg ulcer 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 are considered purely venous if clinically no other aetiology is suspected. The ulcer is required to be venous in appearance (i.e. moist, shallow, of an irregular shape) and was to lie wholly or partially within the gaiter region of the leg.

Appendix 3

Screening assessment
- Consent obtained
- Inclusion and exclusion criteria checked
- Ulcer measured to determine size

Ineligible patients
Anonymised screening data recorded

Eligible patients

Baseline assessments
Clinical assessments: - Digital photo of reference ulcer and tracing. Record of: VAS Pain Score, current medication, medical history, standard care administered (if any), demographic data, contact details for patient and their GP.

Randomisation – to placebo/aspirin
IMP to be collected by patient on next visit to clinic or posted direct to patient.

Weekly assessments for 25 weeks post-randomisation
Healing outcomes – Digital photo of reference ulcer and date taken.
Record of: Treatment concordance (including initially, date trial treatment commenced), adverse events/changes in medical condition, changes to other medication, change in type of dressings used.

4 - 6 weeks post-randomisation
In addition to weekly assessments, participants will be asked about ulcer related pain (VAS pain score).

25 weeks post-randomisation: ***Final assessment*** *of patients whose leg ulcers have been confirmed as healed on or before week 25, or whose leg ulcers are not suspected as healed.*
In addition to weekly assessments, there will be a grid tracing of reference ulcer.
IMP container and remaining medication returned for all trial participants.

26 weeks post-randomisation *(Only patients whose leg ulcers were suspected as healed in weeks 24 and/or 25.)*
Digital photo taken of wound area.
Record of adverse events, changes to other medication and change in type of standard care administered.
(For patients whose leg ulcer was suspected as healed in week 24, an assessment will be made of digital photo to confirm healing.)

27 weeks post-randomisation (*Only patients whose leg ulcers were suspected as healed in week 25*
Digital photo taken of wound area.
Record of adverse events, changes to other medication and change to standard care administered/types of dressings
(Assessment of digital photo to confirm healing).

Reference ulcer judged as healed
Participant to continue with trial medication

1 week after judged as healed
Healing outcomes – Digital photo of reference ulcer and date taken
Treatment concordance
Adverse events
Change to standard care administered/types of dressings.

2 weeks after judged as healed
Healing outcomes – Digital photo of reference ulcer and date taken, and clinical assessment of photo.
Treatment concordance.
Adverse events
Change to standard care administered/types of dressings

Healed
Participant given a card and ask to notify the trial team if wound breaks down. Discontinue trial medication.Remaining medication returned to St George's Research Pharmacy.

Not Healed
Participant continues with trial medication and continues in trial

25 weeks post-randomisation
Research nurse phones patient to ask if new ulcer and to collect adverse event data

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)
			wk1	wk2	wk3	wk4	wk5	wk6	Wks 7-24	wk25	wk26	wk27
Informed consent	X											
Inclusion/exclusion criteria	X	X										
Demographics		X										
Dispensing of IMP			X									
Medical history	X	X										
Concomitant medication	X	X	X	X	X	X	X	X	X	X[1]	X	X
Adverse events/side effects/change to health status			X	X	X	X	X	X	X	X[1]	X	X
Ulcer photograph[2]		X	X	X	X	X	X	X	X	X[1]	X	X
Tracing of ulcer	X	X								X[1]		
Resource use – change to type of usual care/compression bandage administered			X	X	X	X	X	X	X	X[1]	X	X
Compliance with IMP & usual care			X	X	X	X	X	X	X[1]	X[1]		
VAS Score		X				X	X	X				
Phone call to check reoccurrence (only patients whose leg ulcer was confirmed as healed before week 25)										X		

[1]Data will not be collected from patients whose reference leg ulcer healed earlier in the trial.

[2]If a digital photograph of the ulcer cannot be taken then a tracing of the ulcer will be made instead.

Appendix *4.*

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)

VAS score