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DEep VEin Lesion OPtimisation (DEVELOP) Trial. Protocol for a randomised, assessor-blinded feasibility trial of iliac vein intervention for venous leg ulcers

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Study protocol

Keywords: venous ulcer, endovenous, deep venous intervention, iliac vein, intra-vascular ultrasound, great saphenous incompetence

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Abstract

Background: Venous leg ulceration is a widespread, debilitating pathology with high recurrence rates. Conservative treatment using graduated compression dressings may be associated with unacceptable ulcer recurrence rates. Early superficial venous ablation encourages ulcer healing and reduces recurrence. However, many of this cohort display concomitant ilio-caval stenosis, which further contributes to lower limb venous hypertension and ulceration. An approach which combines early superficial venous ablation with early treatment of ilio-caval stenotic disease may significantly improve ulcer healing and recurrence rates. We question whether early iliac vein interrogation with intravascular ultrasound (IVUS), stenting of significant occlusive disease plus superficial venous ablation, in patients with active venous leg ulceration, will produce superior ulcer healing to standard therapy. Methods: This is a prospective, multi-centre, randomised controlled, feasibility trial recruiting patients with lower limb venous ulceration and Great Saphenous incompetence. Patients will be randomised to undergo either truncal ablation and compression therapy or truncal ablation, simultaneous iliac interrogation with intravascular ultrasound and stenting of significant (>50%) iliac vein lesions plus compression therapy. The primary endpoints will be ulcer healing and procedural safety. Secondary endpoints include time to healing, quality of life and clinical scores, ulcer recurrence rates and rates of post-thrombotic syndrome. Follow up will be over a five-year period. This feasibility trial is designed to include 60 patients. Should it be practicable a total of 594 patients would be required to adequately power the trial to definitively address ulcer-healing rates. Discussion: This trial will be the first randomised trial to examine the role iliac interrogation and intervention in conjunction with standard operative therapy in the management of venous ulceration related to Great Saphenous incompetence. Ethical Committee Reference: C.A. 2111 Galway Clinical Research Ethics Comittee Registration: Clinical Trials.gov registration NCT03640689 , Registered 21/08/2018, https://clinicaltrials.gov/ct2/show/NCT03640689

Keywords: venous ulcer, endovenous, deep venous intervention, iliac vein, intra-vascular ultrasound, great saphenous incompetence

Background

Leg ulcers are a widespread, debilitating problem with a prevalence in Ireland of 0.12% overall. This increases to 1% among patients over 70 years of age. Recurrence is common with 12-month healing rates reported between 16% -36% (1). The majority of these leg ulcers (81%) are venous in origin and are treated in the community by public health nurses at a significant annual cost (2).

Typically chronic venous hypertension results in lower limb skin changes, often at the level of the ankle. Oedema, fibrin pericapillary cuffs and/or trapping of white cells within the interstitium typically precede tissue loss with these changes leading to skin ulceration as a result of relative local tissue hypoxia or cytokine/protease release (3,4).

The mainstay of treatment of leg ulcers is the application of graduated compression to the limb with the aim of promoting venous return, reversing venous hypertension and the local tissue changes, thus

allowing the ulcer to heal. Maximum compression is applied at the ankle with gradually lesser compression being applied proximally up the leg. Graduated compression bandaging is usually used to achieve ulcer healing while compression stockings are fitted to prevent recurrence. A Cochrane review of the management of leg ulcers concluded that: compression increases ulcer healing rates compared to no compression, multi-layered systems are more effective than single-layered systems and that high compression was better than low compression (5). Nevertheless, in spite of the application of best evidence-based therapy, healing rates for venous leg ulcers remain disappointing at 50% to 70% following 12 weeks of treatment (6).

With an increasingly elderly population the incidence of venous ulceration is likely to rise. The negative impact of leg ulceration on patients' quality of life and on healthcare costs is well recognised (7-9). Increased prevalence combined with poor reported healing rates and high incidence of ulcer recurrence makes the development of a new treatment which could accelerate healing rates beyond that currently achieved using compression bandaging most desirable.

Methods

2.Trial Rationale:

Traditionally, venous reflux was viewed as the primary causative factor in venous ulceration. Treatment strategies such as compression or, more recently, early superficial venous ablation (10) aim to address the reflux and thereby encourage ulcer healing. However, advances in imaging techniques have revealed that ilio-caval venous obstruction occurs frequently in patients with chronic venous disease (11,12). Moreover, endovascular treatment of ilio-caval occlusive disease produces significant symptomatic improvement even in the presence of persistent uncorrected deep venous reflux (13).

Two recent systematic reviews have concluded that endovascular stent placement for iliac-caval venous obstruction is safe with high technical success rates (14,15). Non-thrombotic iliac vein lesions (NIVLs) are present in up to 80% of patients with symptomatic venous disease (16). These lesions are characterised by their non-thrombotic aetiology and often are identified at post-mortem as intravascular adhesions or membranes. Commonly they are in the form of a web and may progress to venous occlusion or contribute to increased lower limb venous pressures. These obstructive lesions are left unaddressed by ulcer treatment strategies, which focus solely on the reflux component of the underlying venous hypertension. This predisposes to persistent venous hypertension, in turn leading to recurrent superficial venous reflux and an increased risk of recurrent ulceration. This focus solely on the reflux component may explain the relatively limited improvement in ulcer healing rates in studies of early venous ablation (10).

An approach which combines early superficial venous ablation with early treatment of NIVLs i.e. addresses both the reflux and obstructive components of the disease could significantly improve ulcer healing and recurrence rates. Iliac vein interrogation and stenting if appropriate undertaken

simultaneously with superficial venous ablation has the potential to significantly improve ulcer healing rates.

Thus, we ask, that in patients with active venous leg ulceration does early iliac vein interrogation with intravascular ultrasound (IVUS), stenting of significant occlusive disease plus superficial venous ablation produce superior ulcer healing to compression therapy plus superficial venous ablation alone?

3.Objectives:

The single main research question for this trial is as follows: in adult patients with venous ulceration and great saphenous vein incompetence; does iliac vein assessment with IVUS and stenting of significant occlusive disease in addition to superficial great saphenous venous ablation and compression compared to superficial venous ablation and compression alone offer improved ulcer healing rates at three months following treatment?

3.1 Primary Objective

To determine whether superficial venous ablation plus early iliac vein interrogation plus endovascular stenting in the presence of significant occlusive disease results in improved venous ulcer healing compared to superficial venous ablation plus compression therapy alone.

3.2 Secondary Objectives

1. To determine the relative performance of duplex ultrasound compared to IVUS for the prediction of NIVLs
2. To determine the rate of primary or recurrent ulceration up to five years following intervention
3. To assess patient quality of life in the short and medium term following each mode of intervention

4.Trial Design and Endpoints:

4.1 Statement of Design

This is a prospective randomised controlled, assessor-blinded, feasibility trial with participants allocated to one of two parallel groups in a 1:1 fashion. The primary trial centre will be the University Hospital Galway, Ireland with further centres currently being evaluated for inclusion. Both the Departments of Vascular Surgery and Interventional Radiology will conduct the trial in unison with equal oversight. Suitable patients shall be recruited from both the outpatient and inpatient setting.

4.2 Endpoints

4.2.1 Primary Efficacy Endpoints

The primary efficacy end-points will be the proportion of ulcers healed three months following overall intervention and the iliac vein patency in the interventional group.

- A healed ulcer is defined as complete re-epithelialization with no scab and no requirement for dressing (17).

Stent patency will be evaluated by ultrasound within 24-hours, at three-months, one year and annually thereafter. One-year patency rates will be reported alongside the primary efficacy endpoint. Five-year patency rates will be reported in a separate long-term follow-up report. The following will be reported with respect to patency:

- Primary patency: patent stent with less than 20% in-stent or between stent stenosis and no re-interventions
- Primary assisted patency: patent stent with less than 20% in-stent or between stent restenosis which has undergone re-intervention to prevent occlusion
- Secondary patency: patent stent which has been reopened following occlusion
- Stent occlusion: stent with a no-flow segment which has not undergone re-intervention or in which re-intervention failed

4.2.2 Primary Safety Endpoint

The primary safety endpoints in the intervention group are any complications arising from the additional use of IVUS and the requirement for subsequent acute or sub-acute re-intervention (at any time) as a result of the primary intervention.

4.2.2(a) Re-intervention

Freedom from re-intervention will be presented for one-year and five-year follow up reports. Both superficial and deep venous re-interventions will be recorded.

4.2.3 Secondary Endpoints

1. Percentage reduction in ulcer area at 12 weeks, six months and one year
2. Time to ulcer healing (days)
3. Bates-Jensen wound assessment tool (BWAT) (18,19) scores for the index ulcer at six weeks, 12 weeks and six months
4. Changes in Venous Clinical Severity Score (20) at six weeks, three and six months and one year.
5. Number of healthcare contacts in the six months following procedure
6. Changes in EQ5D (21) measures of quality of life at six weeks, 12 weeks, six months and one year
7. Ulcer recurrence following healing of the index ulcer
8. Unplanned hospital admission in six months following procedure

9. Incidence of post-thrombotic syndrome (PTS) at one year as determined by the Villalta Score (22)
10. Health economic analysis based on generated data

5. Trial Population:

5.1 Inclusion Criteria

Consenting patients, aged 18 and over, with ultrasound detected Great Saphenous Venous incompetence with an associated primary or recurrent lower limb venous ulcer(s) will be eligible for inclusion. Great Saphenous reflux is defined as retrograde flow >0.5 seconds in superficial vein (17)

5.2 Exclusion Criteria

1. Ankle-brachial pressure index <0.8
2. Previous inability to tolerate lower limb compression bandaging
3. Inability to provide informed consent
4. Previous lower limb arterial revascularisation procedure
5. Contrast allergy
6. Previous history of pelvic malignancy or pelvic radiotherapy
7. Pregnancy
8. Previous iliac vein intervention
9. Previous superficial vein intervention
10. Infection in previous 30 days
11. Estimated glomerular filtration rate (eGFR) < 60 mls/kg/min
12. Isolated short saphenous or perforator vein reflux only
13. Leg ulcer of non-venous aetiology (as assessed by clinician)
14. Unfit for endovascular intervention based on history and examination

5.3 Informed consent of the inpatient

The process of obtaining informed consent will be conducted in compliance with the principals of good clinical practice and requirements of the approving research ethics committee. Consent to enter the trial will be sought from each subject only after a full written and verbal explanation has been given and appropriate time allowed for consideration. Signed subject consent will be obtained and a copy given to the subject. It is a right of the subject to refuse to participate or to withdraw at any time from the protocol without giving reasons and without prejudicing treatment.

5.3.1 Informed consent of the outpatient

Eligible patients will be given an information sheet at their outpatient visit and the trial will be explained to them by a team member. The patients will be contacted by telephone after a period of seven days to

determine if they are willing to take part. An anaesthetic pre-assessment visit will be required. Written informed consent will be obtained immediately before the procedure.

5.4 Randomisation

Following the consent process randomisation will be undertaken using sequentially numbered opaque sealed envelopes administered by an independent research assistant in the Lambe Institute, University Hospital Galway allowing for allocation concealment. A unique trial number will be assigned to each individual at the time of randomisation. Patients will be randomised to one of two groups.

Group 1:Compression bandaging and endovascular treatment of superficial great saphenous incompetence.

Group 2:Compression bandaging, endovascular treatment of superficial great saphenous incompetence with simultaneous iliac vein interrogation with IVUS and stenting if an occlusive lesion ≥50% is identified.

A designated member of the research team who will not be involved with data collection will have access to the randomisation data and arrange intervention and investigation as required. There will be no sham intervention.

5.5 Baseline patient data

Patients will all have a full medical history taken and clinical examination as part of their standard care. The following will be recorded:

1. Weight
2. Height
3. Blood pressure
4. Heart rate
5. ECG
6. Gender
7. Ethnicity
8. Date of birth
9. Diabetes mellitus
10. Hypercholesterolaemia
11. Hypertension
12. Previous myocardial infarction
13. Previous coronary revascularisation
14. Previous stroke
15. Atrial fibrillation

16. Peripheral arterial disease
17. Smoking history
18. NYHA class
19. Medication at time of consent (aspirin, clopidogrel, beta-blocker, calcium-channel antagonist, nitrates, cholesterol-lowering agent, ACE inhibitor / A2 receptor antagonist, insulin, metformin, sulphonylurea, warfarin)
20. Duration of ulcer prior to enrolment in trial
21. Venous Clinical Severity Score/EQ5D

5.5.1 Ulcer assessment

The ulcer will be evaluated by an assessor who has been blinded to the treatment allocation of the patient. Wound size will be calculated using digital planimetry and recorded as cm^2. Wound assessment will be evaluated using the Bates-Jensen wound assessment tool which has been validated for use in venous leg ulcer assessment (18,19).

5.5.2 Ankle Brachial Pressure Index

All patients will have an ankle-brachial pressure index calculated using a handheld Doppler and a manual sphygmomanometer.

5.5.3 Duplex Ultrasonography

As part of routine clinical care, all patients with a venous leg ulcer undergo a lower limb venous duplex ultrasound. This will assess both the deep and superficial venous systems of the affected leg (including the iliac veins). The results from this scan will be used as the baseline pre-treatment lower limb duplex result.

6. Interventions:

6.1 Endovenous ablation & IVUS procedure

All procedure will be carried out by either a vascular surgeon or interventional radiologist with significant experience in both endovenous ablation and IVUS (Visions 0.035, Philips, Amsterdam). The aim is for ablation within four weeks of randomisation. All patients will undergo endovenous ablation of refluxing axial superficial veins in the affected leg using either the mechanic-chemical ablation (Clarivein, Vascular Insights, Quincy, MA) or radiofrequency ablation (ClosureFast, Medtronic, Dublin, Ireland) under local anaesthesia. The procedures will be undertaken in an ambulatory care setting, operating theatre or in the interventional radiology suite.

The ablation procedure will be slightly modified in order to facilitate IVUS. A 9F access sheath will be placed under ultrasound guidance in the greater saphenous vein (GSV) at knee level to allow introduction

of firstly the IVUS catheter into the ipsilateral common iliac, external iliac and common femoral veins followed by the ablation probe. Iliac vein interrogation using the IVUS will be undertaken to determine the degree of area luminal area reduction (LAR) at each of the known arterial and ligamentous crossing points on the affected side which predispose to NIVL formation. These include the left and right proximal common iliac veins (where crossed by the right iliac artery), the right and left proximal external iliac vein (where crossed by the external iliac arteries and the retro-inguinal regions.

Table 1: Normal anatomical reference values for deep veins

Vein	Normal minimum diameter	Normal minimum area
Common iliac vein	16mm	201mm^2
External iliac vein	14mm	154mm^2
Common femoral vein	12mm	113cm^2

The LAR will be determined by comparison of the minimal luminal area at the NIVL site to the anatomical minimum for the respective vein, as recommended by experts in the field [23]. Area will be calculated using the standard mathematical formula Area = A=πr^2. The reference area values for the iliac veins and the common femoral veins are detailed in Table 1. Lesions will be classified into degree of stenosis by luminal area as detailed in Table 2.

Table 2: Degree of stenosis based on luminal area

Vein	<20% Stenosis	20 to 49% stenosis	50 to 69% stenosis	>70% stenosis
Common iliac vein	≥161mm^2	160 to 103 mm^2	102 to 62mm^2	≤61mm^2
External iliac vein	≥123mm^2	122 to 79mm^2	78 to 48 mm^2	≤47mm^2
Common femoral vein	≥90mm^2	89 to 58mm^2	57 to 35mm^2	≤34mm^2

Patients with a stenosis <50% on the affected side will not have any further iliac or common femoral vein procedure performed. They will undergo endovenous ablation via the previously placed sheath in the great saphenous vein at the knee. Patients with a lesion ≥ 50% will undergo iliac vein stenting (VICI Venous Stent, Boston Scientific, Marlborough, USA) with subsequent great saphenous ablation. All residual varicosities shall be treated with foam sclerotherapy using 1% polidocanol. Foam will be standardised with 1:4 polidocanol to air ratio with 2ml's administered to each varicosity.

7. Compression:

7.1 Compression Therapy

All groups will have four or two-layer compression (Profore, Smith and Nephew, U.K./ Coban,3M, USA) bandaging applied upon initial review once arterial supply is deemed adequate. All patients will be placed in two-layer bandaging immediately post-procedure which will be replaced with a four–layer bandage within 48 hours. Specialist nurses in wound management will subsequently manage compression bandaging in the community with regular review by a vascular surgeon.

8. Schedule of Events:

8.1 Follow up

All patients will be fully assessed at week 6 and 12. Further assessments will be undertaken at 6 and 12-months and annually thereafter. Follow up will be carried out by assessors blinded to the initial intervention.

8.2 Ulcer Assessment

Baseline assessment will be conducted as described in section 5.4.1.

The following end-points will be evaluated at each visit:
a. Integral of the relative ulcer size (area) for each patient over time, standardised to an initial size of 1.
b. Duration until complete wound closure
c. Assessment of wound edges Assessment of granulation (BWAT)
d. Assessment of exudation (BWAT)
e. Assessment of wound edges (BWAT)
f. Assessment of undermining (BWAT)
g. Assessment of wound bed tissue (BWAT)
h. Maximum pain in 22 hours previous to each visit (0 to 100 VAS)

8.3 Venous Clinical Severity Score

The Venous Clinical Severity Score will be completed at six and twelve-weeks initially with further assessment at six-months and annually thereafter until five-year follow-up is complete.

8.4 EQ5D Questionnaire

Quality-of-life will be evaluated by completion of the EQ5D form at six weeks and twelve- weeks, six months and annually thereafter until 5 year follow-up is complete. This data will be further utilised to generate health economic data.

8.5 Healthcare contacts diary

Each participant will be provided with a diary following their venous ablation procedure in order to record all planned and unplanned healthcare contacts (GP visits, public health nurse visits, emergency department visits, hospital admissions, outpatient visits). The patients will be asked to fill out the diary until their six-month visit.

8.6 Iliac stent follow up

Patients who undergo iliac vein stenting alone will undergo follow up iliac vein colour duplex in the radiology department at 1 day, 6 months, one year and annually thereafter. Reflux duration, stent patency, stent fracture, in-stent or between stent restenosis will be recorded at each visit. Due to the nature of this surveillance it will not be possible to blind the ultrasonographer who will not be involved in trial protocol.

8.7 Superficial venous ablation surveillance

All patients undergoing endovenous ablation will undergo duplex ultrasound assessment of the treated great saphenous vein at six weeks and six months to assess for recanalisation.

8.8 Incidence of Post-Thrombotic Syndrome

The incidence of PTS will be determined for each group at one year and five years. The presence and severity of PTS will be assessed using the Villalta score, consisting of five patient-rated leg symptoms (pain, cramps, heaviness, paraesthesia, and pruritus) and six physician-rated clinical signs (pretibial oedema, skin induration, hyperpigmentation, redness, venous ectasia, and pain on calf compression). For each item, a score of 0 (none) to 3 (severe) points will be given and points summed into a total score (range 0 to 33). The absence of PTS will be defined by a total score of <5. PTS will be further classified as mild (total score 5–9 points), moderate (10–14 points), or severe 17 (≥15 points or presence of a venous ulcer).

8.9 Crossovers

Any crossovers between treatment groups shall be highlighted and reported in the final report.

8.10 Withdrawals during follow up

An individual is free at anytime to withdraw from the trial for any reason without any prejudice as to subsequent therapy. The principal investigator may withdraw and individual from the trial should they be

subject to an adverse event whereby it is in the patients best interest to be withdrawn or should they meet any of the exclusion criteria.

8.11 Loss to follow up

Prior to consent participants will be educated as to the importance and timing of the follow up protocol. Post intervention regular patient contact in the community through specialist nurses will allow for a continued patient dialogue regarding follow up. Should follow up appointments be missed investigators will endeavour to contact patients by phone or via community liaisons to ensure timely follow up within trial protocol. All losses to follow up and its cause shall be recorded and reported in any trial data.

8.12 Protocol Violations

The following will be deemed violation of protocol and result in removal from the trial

1. Non-compliance with compression therapy despite adequate patient education
2. Failure to undergo ablation therapy within six weeks

8.13 Premature termination of the study

The trial may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for trial suspension or termination will be provided to the regional ethical committee and all trial investigators by the principal investigator.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

8.14 Schedule of Events

(SPIRIT table: Appendix 1)

9. Safety Parameters:

9.1 Potential adverse events related to intervention

Primary safety endpoints include the need for re-intervention and stent patency. The risk of

any significant adverse event occurring is deemed unlikely however all reasonable measures

to avoid these events will be undertaken. Any adverse events (as described below) will be recorded and reported in any trial data.

1. pain
2. bleeding
3. infection
4. phlebitis
5. nerve injury (temporary/permanent)
6. incomplete ablation of targeted superficial vein
7. recurrence of ulceration
8. deep venous thrombosis
9. pulmonary embolism
10. adverse reaction to local anaesthetic
11. iliac vein injury
12. failure of stenting procedure
13. pressure ulceration from dressings
14. contrast induced renal injury
15. stent occlusion

9.2 Definition of an adverse event

Any untoward medical event related directly or indirectly to an intervention as a result of participation in the trial.

9.3 Definition of a serious adverse event

Any event that results in death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect is deemed a serious adverse event.

9.4 Event Reporting

All adverse events will be reported directly to the either the site or principal investigator. Recurrent adverse events or serious adverse events in isolation will be reported in turn to the local ethical committee and the risk assessment department for risk analysis. Indications for premature trial cessation are discussed in section 8.11.

10. Statistical considerations:

Once randomisation and intervention is complete patient outcomes will be assessed using an intention-to-treat analysis. All losses to follow up at any time-point will be recorded and reported. A research statistician will conduct all analyses independently. Statistical analysis will conducted using SPSS Version 21 (IBM Corp, Aramonk, N.Y.) Descriptive data will be provided at baseline and at each follow up to define variations among and within groups. Continuous data will be presented as mean and standard deviations with confidence intervals of 95%. Categorical data will be reported as frequencies with chi-square or Fischer's exact t-test used for comparative data. Where data is not normally distributed non-parametric will be utilised as applicable. A p-value of <0.05 will be deemed significant.

Contemporary data suggests a median healing time of about 20 weeks for patients with a venous ulcer treated by superficial venous ablation [24]. Assuming a median time to healing in the control arm (those treated with superficial venous ablation and compression alone) of 140 days would be reduced to 110 days by the addition of iliac vein intervention where necessary (i.e. a 20% relative reduction in healing time) would require 270 patients in each arm of the trial i.e. 540 in total. Allowing for a 10% withdrawal and dropout rate increases the required sample size to 594 patients. In advance of undertaking such a large trial, we aim to undertake a feasibility phase in order to assess eligibility, recruitment rates and provide baseline data for a refined sample size calculation. For this feasibility phase, we aim to recruit 30 patients to each arm of the trial i.e. 60 patients in total.

10.1 Interim Analysis

Once 60 patients have been recruited and followed up for six-months an interim analysis shall be undertaken to guide recruitment and further inform trial design with a view to powering the trial appropriately.

11. Ethical Considerations:

11.1 Ethical approval

Ethical approval has been approved centrally by the Galway Clinical Research Ethics Committee, Galway, Ireland. The ethics committee reference is C.A. 2111. Of note recruitment shall not commence at any other centre until full ethical approval has been confirmed with the local ethical committee.

11.2 Data Protection

All data shall be managed in the strictest confidence by approved trial investigators in accordance with Irish data-protection law. Datasets will be anonymous, encrypted and stored onsite only.

Discussion

The management of lower limb venous ulceration continues to raise significant debate particularly, in more recent years, with regard to adjunctive surgical intervention. At present conservative measures including regular ulcer dressing with compression bandaging are well established. This approach offers

undoubted benefits improving both ulcer healing rates and reducing recurrence (5,25) in the longer term. However, this approach can be slow with a median ulcer healing time of up to 99 days (5) and high rates of non-compliance (25). As such, more efficient treatment protocols continue to be investigated.

The recent publication of the EVRA trial (17) has further enhanced the concept that early surgical intervention can improve treatment protocols in the venous ulcer cohort. Included patients randomised to the intervention group of early endovenous intervention in conjunction with compression therapy experienced a significantly shorter time to ulcer healing. The authors identified a median ulcer healing time of 56 days in the treatment group compared to 82 in the control group among 450 patients. Furthermore, they identified an impressive overall healing rate of 85.6% at 24-weeks compared to 76.3%. This data consolidates evidence from the ESCHAR study (26) which confirmed lower ulcer recurrence rates at 12-months following combined intervention with surgery and compression therapy. As a result of these data a combined approach to venous ulceration is now widely advocated. (27)

Thus, while it would appear that dual intervention offers benefit to ulcer patients a significant proportion of those affected may have concomitant NIVL's (16) contributing to the venous hypertensive pathophysiology. This further exposes patients to delayed, non-healing and recurrent ulceration. At present these lesions go largely unnoticed due to inadequate peri-operative imaging with access to MRV and CTV often resulting in further treatment delays and the added risks of contrast exposure. Intravascular ultrasound offers proven (28), minimally invasive imaging of the ilio-femoral segment simultaneously with superficial venous ablation. This provides the treating physician with a real-time assessment of NIVL's and the ability to concomitantly treat significant lesions thus reducing risk of persistent venous hypertension.

This randomised controlled feasibility trial aims to provisionally assess the merits and safety of adjunctive procedural IVUS, stenting, endovenous ablation and compression therapy in the treatment of venous ulceration. To date there is a paucity of data addressing this important health issue and consequently there is a need for well-designed large randomised studies examining the hypothesis.

Due to the significant number of patients required to adequately power this trial an initial feasibility trial on 60 patients will be carried out. This period will be used to assess trial flow, recruitment and the initial efficacy of treatment. Should the initial trial be successful the authors plan a multi-centre approach to allow for adequate and timely patient recruitment and treatment with a view to definitively identifying the role of iliac intervention in this cohort.

Status of trial:

Protocol: 1. V8

Recruitment: Commencing July 2019

Estimated Completion: July 2020

Abbreviations

ABPI	Ankle brachial pressure index
CT	Computed Tomography
eGFR	Estimated glomerular filtration rate
LAR	Luminal area reduction
MR	Magnetic resonance
NIVL	Non-thrombotic iliac vein lesion
PTS	Post-thrombotic Syndrome
BWAT	Bates-Jensen wound assessment tool
IVUS	Intravascular ultrasound

Declarations

Ethics approval and consent: Ethical approval has been granted by the Galway Clinical Research Ethics Committee Galway, Ireland. Ethics reference number C.A.2111. Consent will be sought from each individual participant prior to inclusion. Full verbal and written information will be provided. Participants reserve the right to refuse with no reason provided and this will not bias their treatment. Participants are free to withdraw at any time.

Consent for Publication: Consent for publication shall be sought during the initial participant consent process for trial inclusion. (Appendix 2)

Availability of data and materials: Anonymous data and materials will be encrypted and stored in the secure server within the Lambe Research Institute, National University of Ireland. Data will be available upon suitable request to the senior author.

Competing Interests: The authors declare no competing interests

Funding: There is no funding in place for the completion of this trial

Author Contributions:

TA: Writing, concept, review

CK: Writing, Review

MM: Concept, Writing, review

GO'S: Concept, review

SB: Design, review

TT: Design, review

SW: Writing, concept, design, review

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Figures

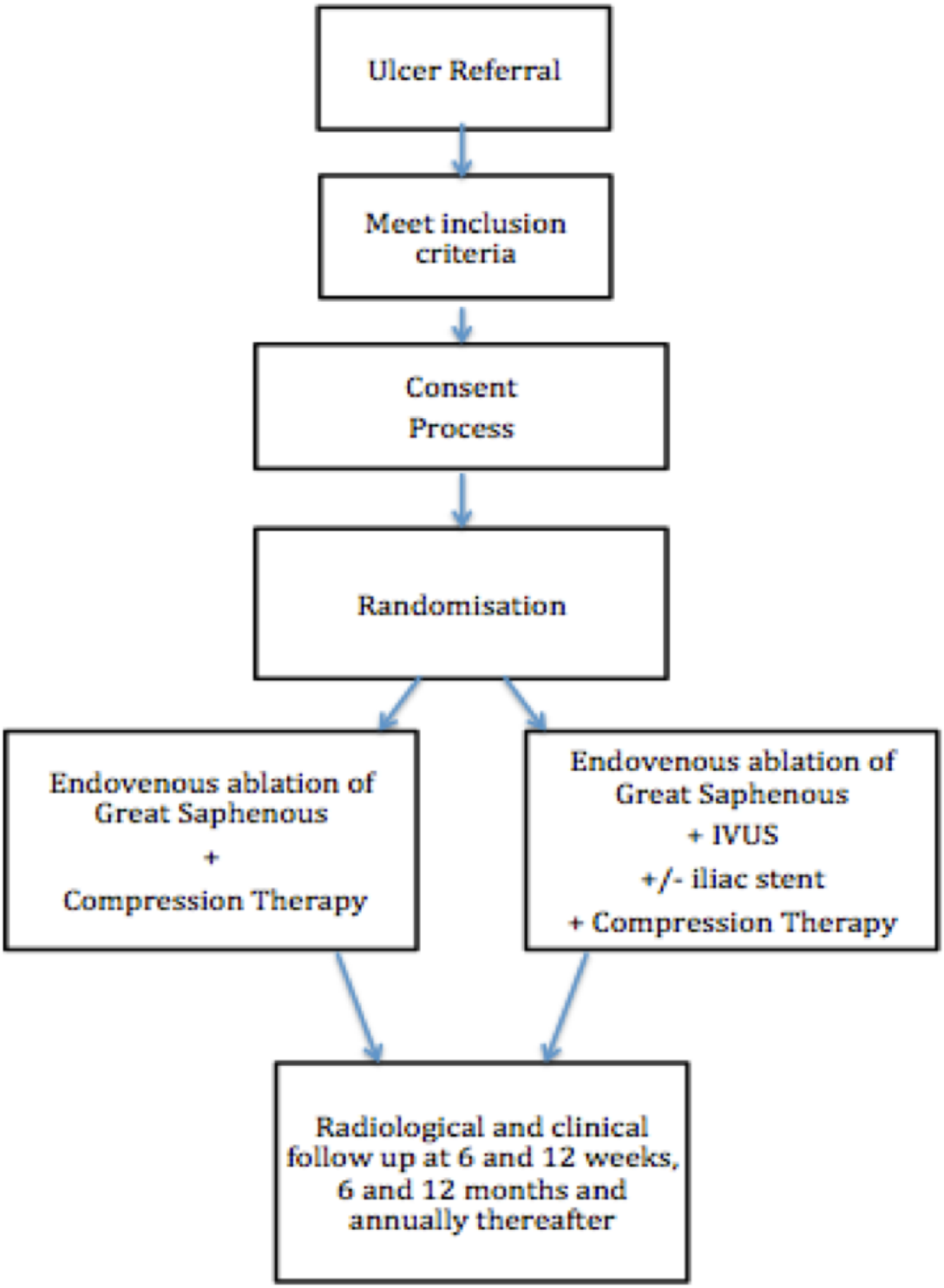

Figure 1

Schematic of Study Flow.

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