Imperial College London

Research Governance and Integrity Team

Imperial College Healthcare NHS Trust

Template Protocol for non-CTIMPs

Estimating & comparing the performance, clinical effectiveness, and cost-effectiveness of current diagnostic options for patients that present to primary care with suspected venous ulcers.

Version 7.0, 18/02/2025

MAIN SPONSOR: Imperial College London
FUNDERS: N/A
STUDY COORDINATION CENTRE: N/A

IRAS Project ID: 326810
REC reference: N/A
NCT: 06181708

Protocol authorised by:

Name & Role	Date	Signature

Study Management Group

Chief Investigator: Professor Alun Davies

Co-investigators: Emma Flint PhD student

Clinical Queries

Clinical queries should be directed to Emma Flint, e.flint1@nhs.net who will direct the query to the appropriate person

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Research Governance and Integrity Team
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
Norfolk Place
London, W2 1PG
Tel: **0207 594 1862**
Imperial College - Research Governance and Integrity Team (RGIT) Website

Funder

This study is unfunded.

This protocol describes the Estimating & comparing the performance, clinical effectiveness, and cost-effectiveness of current diagnostic options for patients that present to primary care with suspected venous ulcers study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Table of Contents

GLOSSARY OF ABBREVIATIONS

CVD	Chronic venous disease
CVI	Chronic venous insufficiency
VLU	Venous leg ulcer
ABPI	Ankle brachial pressure indices
NICE	National Institute of Care and Excellence

KEYWORDS
Chronic venous disease
Chronic venous insufficiency
Venous leg ulcers
Diagnostics
Vascular Scientists
Delphi
Cost effectiveness

STUDY SUMMARY

TITLE	Estimating & comparing the performance, clinical effectiveness, and cost-effectiveness of current diagnostic options for patients that present to primary care with suspected venous ulcers.
DESIGN	Online questionnaire . survey study
AIMS	The main objective of this project is to determine the role/position of diagnostic imaging in the patient journey for a patient with active or healed ulceration.
OUTCOME MEASURES	To determine the minimum diagnostics that any patient that presents to primary care with a suspected venous ulcer should receive. Assess the cost effectiveness of implementing these established diagnostics into different care models.
POPULATION	Primary care health professionals and vascular scientists.
ELIGIBILITY	Primary care practitioners working in the UK and vascular scientists working in secondary care in the UK.
DURATION	20 months

1. INTRODUCTION

1.1. BACKGROUND

Chronic venous disease (CVD) encompasses a broad spectrum of venous abnormalities in which there is a significant compromise in the return of blood to the heart. CVD is both prevalent and progressive in nature (Ortega et al. 2021). CVD refers to complications that arise in the lower extremity due to retrograde (reverse) venous flow, also known as chronic venous insufficiency (CVI) which is caused by a persistent elevation in venous pressures, commonly referred to as venous hypertension (Millan et al. 2019). There are multiple potential causes of venous insufficiency and fundamentally venous hypertension. The clinical presentation of CVI can vary depending on the severity of the disease, with the most severe cases presenting with leg ulceration (Escudero Rodriguez et al. 2014). NICE define a venous leg ulcer (VLU) as a loss of skin that take more than 2 weeks to heal due to sustained venous hypertension (NICE 2021). Other definitions include a breach in the epithelial integrity of the skin occurring between the knee and malleoli (Poskitt and Gohel 2019). The typical location and most common presentation of VLUs is the medial gaiter area of the leg, however lateral and foot ulceration may also occur and be associated with venous insufficiency and or hypertension (Poskitt and Gohel 2019).

Leg ulcers contribute to a huge socio-economic impact on the NHS annually, with over an excess of 100,000 active leg ulcers in the UK at any one time (Cunliffe 2021). They have been documented to be a significant burden on healthcare systems internationally and particularly in association with primary and community care. In addition to the associated extreme cost burden, they are associated with detrimental effects on patients quality of life, causing pain, discomfort and overall distress to the patients (Alguire and Mathews 1997; Barwell et al. 2000).

Currently there is a wide variation in practice of leg ulcer management leading to a discrepancy in treatment that patients are receiving. Data collated from the Health Improvement Network database has shown that more than 90% ulcers remained unhealed at 6 months (Guest et al. 2012). This, alongside other supporting reviews, leads to questions of these alarmingly low healing rates (White et al. 2013). Evidence suggests that this cohort of patients are being managed sub optimally in primary care and a more standardized approach needs to be taken to improve overall ulcer healing rates and ulcer prevent recurrence. Dressings alone will not heal these ulcers and prevent recurrence, the underlying cause of these ulcers must be determined and this cause treated (Cunliffe 2021).

Diagnostics play an important role in the management of venous leg ulceration with multiple literature sources emphasising the importance of diagnostic testing to confirm a diagnosis of venous insufficiency, to determine the aetiology, localise the anatomical site and level / source of disease (O'Donnell et al. 2014; DeMaeseneer et al. 2022). Duplex ultrasound is a non-invasive, cost effective and a reproducible imaging modality commonly used determine the source of venous insufficiency and to map the venous system (Alguire and Mathews 1997). It is believed that to perform the correct and necessary venous interventions procedures, a venous duplex ultrasound scan should be performed to delineate the source or reflux and all potential reflux targets (O'Donnell et al. 2014). To further support this, early endovenous ablation of superficial vein reflux has been shown to result in faster healing of

venous leg ulcers and a longer period of ulcer free time, compared to those that received delayed endovenous ablation (Gohel et al. 2019).
Primary care has limited resources for performing diagnostic investigations for suspected venous leg ulcers and limited appropriately trained staff to manage these patients. Additionally, the pathway for onward referral to a specialist ulcer service are variable and vary by geographical location (NHS England 2018).
In the UK, currently the only diagnostic test mentioned in the NICE guidelines with regards to managing these patients is an ABPI. This test is to determine the state of a patients arterial blood supply and therefore the suitability of these patients to go into compression bandaging (NICE 2021). Patients presenting with leg ulcers are therefore receiving different diagnostic, management, and treatment pathways and most importantly, they are al receiving this care at different time intervals depending on where they present.

1.2. RATIONALE FOR CURRENT STUDY

The pathway of current practice from the patient first presenting to receiving this treatment, including vascular diagnostics, has not been investigated in detail, and is therefore not optimised. There is a lack of evidence and written documentation regarding diagnostics in the available guidelines. This means that there is a lack of standardised care for this cohort of patients across the UK.

It is hypothesised that by understanding how primary care currently refer onto specialist centres and establishing a consensus on what diagnostic tests should be performed on this cohort of patients, a conclusion on the most cost and clinical effective method of delivering diagnostics and care to this cohort of patients can be established. It is hypothesised that this will involve generating clearer guidelines and standardised pathways based on up-to-date literature for when VLU patients initially present into primary care, including when they should be referred onto specialist vascular centres, what specific diagnostic tests should be performed upon initial presentation and an outline of treatment options. The most cost-effective method may also suggest the initiation of specialist leg ulcer clinics involving a multidisciplinary team.

2. STUDY OBJECTIVES

The aim of this project is to determine the minimum diagnostics that any patient that presents to primary care with a suspected venous ulcer should receive and look at the most effective way to implement this.

Primary Objective

1) To determine the role/position of diagnostic imaging in the patient journey for a patient with active or healed ulceration.

Secondary Objective

1) To determine the current practice in primary care for venous ulcer management.
2) To determine the current practice for diagnosis and management of suspected venous leg ulcers in vascular scientist departments across the UK
3) To establish what the minimum diagnostics should be for this cohort of patients including what scans should be performed and can a set criterion be applied to this cohort of patients.
4) To determine the cost effectiveness of implementing this in both primary and secondary care settings.

3. STUDY DESIGN

1) To determine the current practice of primary care, a questionnaire will be designed using Qualtrics management platform (Qualtrics, UT, USA) to assess various aspects of the national management and diagnostics for venous leg ulceration. A similar methodology will be utilised to that of a previous primary care questionnaire that was disseminated to primary care practitioners pre and post the EVRA trial (Heatley et al. 2020). Key areas to be investigated will be whether there are one main set of guidelines that primary care practitioners follow, the availability of services they have in their centre and if they have any major barriers to onward referrals. The questionnaire is attached, it has been tested and optimised after engagement with key stakeholders.
2) To determine the current diagnostic pathways for this cohort of patients in vascular departments across the UK and to try and establish a uniform standardised diagnostic pathway, a Delphi consensus will be performed amongst vascular scientists. Responses will be summarised between each round and fed back to the participants. This will be used to determine a consensus on the best and most realistic diagnostic management of these patients. For the purpose of this study, a consensus has been defined at a ≥70% agreement. The hope is that by involving those that could be directly implicated by any changes to the guidelines, it will initiate interest and engagement both during the consensus itself and implementing the findings of the consensus. The first round of the Delphi questionnaire is attached, it has been tested and optimised after engagement with key stakeholders.
3) To investigate whether there is a minimum diagnostic that can be recommended for this cohort of patients the current literature regarding typical pattern of reflux and anatomical location of ulcers will be reviewed. This may involve details on who should perform and where these investigations should or could be performed. To determine whether there is a minimum number of diagnostic investigations that needs to be carried for these patients, in conjunction with the results from the Delphi consensus, a detailed literature review will be carried out looking into the location of venous ulcer and source of reflux. This will be done by initially identifying PICOS criteria. I will then develop a search strategy and input this into Ovid. From the papers identified in this search, I will perform abstract screening against the pre-defined PICOS criteria, complete full text screening, data and information extraction, analysis, and synthesis. This is to determine whether all patients require a full venous

duplex scan, or whether in some situations, a quicker less detailed 'spot check' scan can be performed. This in turn will also contribute valuable information regarding the setting for the diagnostic testing.

4) To establish the cost effectiveness of different proposed models, a Markov model will be constructed to estimate the health outcomes and costs over 5 years of different testing strategies applied to a cohort of VLU patients. Variations of diagnostic tests combinations and settings to be investigated may include, ABPI in primary care and full venous duplex in secondary care, ABPI and venous duplex in primary care, ABPI and venous duplex in secondary care. Health outcomes will be venous ulcer healing rates and venous ulcer recurrence rates. Sensitivity analyse will also be performed (Normahani et al. 2021; Epstein et al. 2018).

3.1. STUDY OUTCOME MEASURES

1) The electronic questionnaire to primary care networks will be shared via various social media platforms and will remain open for 1 months for responses. The questionnaire will be reposted at regular intervals to promote engagement.
2) The Delphi consensus will continue until a consensus has been reached, ≥70% agreement. Each round of the consensus will be open for one month. Response analysis and design and dissemination of the next round will occur within two weeks.

4. PARTICIPANT ENTRY

4.1. PRE-REGISTRATION EVALUATIONS

N/A

4.2. INCLUSION CRITERIA

Primary care practitioners working in the UK will be recruited for the primary care questionnaire.
Vascular scientists working in a secondary care hospital in the uk will be recruited for the online delphi consensus.

4.3. EXCLUSION CRITERIA

Participants not meeting the inclusion criteria.

4.4. WITHDRAWAL CRITERIA

A participant may withdraw at any time by notifying the researcher Via email: e.flint1@nhs.net
If a participant wishes to withdraw from the primary care study, any data collected up until that time will be kept for analysis.
If a participant wishes to withdraw from the Delphi consensus, they will no longer receive further questionnaires, however any data collected up until that time will be kept for analysis.

5. ASSESSMENT AND FOLLOW-UP

There will be no formal assessment or follow-up in this study.

Definition of end of study:
The study will end when he primary care questionnaire has been live for one month and when a consensus has been reached amongst vascular scientists, defined as a >70% agreement.

6. STATISTICS AND DATA ANALYSIS

A series of descriptive statistics will be carried out on the results obtained from the questionnaire and consensus. Advice will be sought from John Norry, The University of Edinburgh.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study

7. REGULATORY ISSUES

7.1. ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the xxx Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

7.2. CONSENT

Consent will be taken online via Qualtrics. All participants will have access to an online participant information sheet before agreeing to the online consent. The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the protocol without giving reasons.

7.3. CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Data from the primary care and Delphi questionnaires will be pseudonymised.

7.4. INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study

7.5. SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

7.6. FUNDING

This study is not funded.

7.7. AUDITS

The study may be subject to audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

8. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Emma Flint, e.flint1@nhs.net.

9. PUBLICATION POLICY

The results will be included in the final clinical doctorate thesis. The results will be published in peer reviewed journals, conference papers and research presentations. The anonymity of the participants will be ensured when publishing.

10. REFERENCES

Alguire, P. and Mathews, B. (1997). Chronic venous insufficiency and venous ulceration. *Journal of General Internal Medicine*, 12(6), pp.374–383.
Barwell, J.R. et al. (2000). Risk factors for healing and recurrence of chronic venous leg ulcers. *Phlebology*, 15(2), pp.49–52.
Cunliffe, T. (2021). Primary care dermatology society - Leg ulcers. [online]. Available from: https://www.pcds.org.uk/clinical-guidance/leg-ulcers [Accessed October 1, 2021].
DeMaeseneer, M. et al. (2022). Editor's Choice – European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs. *European Journal of Vascular and Endovascular Surgery*, 63(2), pp.184–267. [online]. Available from: https://doi.org/10.1016/j.ejvs.2021.12.024.
Epstein, D. et al. (2018). Cost-effectiveness of treatments for superficial venous reflux in patients with chronic venous ulceration. *BJS Open*, 2(4), pp.203–212.
Escudero Rodriguez, J., Fernandez Quesada, F. and Bellmunt Montoya, S. (2014). Prevalence and clinical characteristics of chronic venous disease in patients seen in primary care in Spain: results of the international study Vein Consult Program. *Cirugia espanola*, 92(8), pp.539–546.
Gohel, M. et al. (2019). A randomized trial of early endovenous ablation in venous ulceration: a critical appraisal. *British Journal of Dermatology*, 180(1), pp.51–55.
Guest, J. et al. (2012). Relative cost-effectiveness of a skin protectant in managing venous leg ulcers in the UK. *Journal of wound care*, 21(8), pp.389–398. [online]. Available from: https://pubmed.ncbi.nlm.nih.gov/22885312/ [Accessed October 1, 2021].
Heatley, F. et al. (2020). Primary care survey of venous leg ulceration management and

referral pre-EVRA trial. *British Journal of Community Nursing*, 25(December), pp.S6–S10.
Millan, S.B., Gan, R. and Townsend, P.E. (2019). Venous ulcers: Diagnosis and treatment. *American Family Physician*, 100(5), pp.298–305.
NHS England. (2018). NHS England » Improving venous leg ulcer healing in the community. *Leading Change, Adding Value*. [online]. Available from: https://www.england.nhs.uk/atlas_case_study/improving-venous-leg-ulcer-healing-in-the-community/ [Accessed October 1, 2021].
NICE. (2021). Leg ulcer - venous. [online]. Available from: https://cks.nice.org.uk/topics/leg-ulcer-venous/ [Accessed October 1, 2021].
Normahani, P. et al. (2021). Cost-Effectiveness of Diagnostic Tools to Establish the Presence of Peripheral Arterial Disease in People with Diabetes. *Annals of Surgery*, Volume pub.
O'Donnell, T.F. et al. (2014). Management of venous leg ulcers: Clinical practice guidelines of the Society for Vascular Surgery® and the American Venous Forum. *Journal of Vascular Surgery*, 60(2), pp.3S-59S.
Ortega, M.A. et al. (2021). Understanding chronic venous disease: A critical overview of its pathophysiology and medical management. *Journal of Clinical Medicine*, 10(15), pp.1–42.
Poskitt, K. and Gohel, M. (2019). Chronic ulceration of the leg. *Surgery (United Kingdom)*, 37(2), pp.88–92.
White, R., Brown, A. and Whayman, N. (2013). Nonhealing venous leg ulcers in primary care: Clinical significance of training, knowledge, treatment, and healing. *Wounds UK*, 9(1), pp.12–14.