RESEARCH QUESTION / TITLE

What is the optimal strategy for the development of a platform for the delivery of trials evaluating the clinical and cost effectiveness of interventions for venous leg ulcer (VLU) prevention and healing?
Title: Venous leg ulcErs: management and eradIcatioN – the VEIN Platform study.

BACKGROUND AND RATIONALE

Venous leg ulceration (VLU) is the most severe manifestation of venous disease. It is estimated that at least 200,000 individuals seek help for these ulcers annually. Epidemiological studies suggest 1% of the population is affected, increasing to up to 4% in those over 65 years o f age(1). VLU places a tremendous burden on the healthcare service and society in terms of time, with district nurses spending large amounts of time caring for ulcers, and in terms of cost, with VLU costing up to £1.3 billion of the annual healthcare budget(4). The prevalence of disease is expected to increase as a function of the ageing population(6). VLU can have a devastating impact on quality of life and patients often suffer with depression, chronic pain, sleeplessness and social isolation(2). The management of VLU presents a considerable burden itself, with the requirement for compression and frequent dressing changes causing disruption to patient lives. Compliance with such treatment is challenging for both patients and carers.

EVIDENCE EXPLAINING WHY THIS RESEARCH IS NEEDED NOW

Despite its burden, VLU has not been at the fore of cardiovascular research prioritisation, with attention having historically concentrated on arterial disease. This is now changing. The James Lind Alliance (JLA) Priority Setting Partnership ran a national survey across clinicians, patients and carers to identify the most important research priorities in vascular disease, with VLU priorities featuring highly(7,8). The All-Party Parliamentary Group on Vascular and Venous Disease recently published a report aptly named 'Venous leg ulcers: a silent crisis' highlighting that patients with VLU are not receiving the care that they need(4). Because of its complex nature, VLU healing and prevention could be supported by a variety of approaches, including conservative (lifestyle changes, exercise, compression), medical (pharmacotherapy) and surgical (superficial, deep venous intervention). Despite a sizeable body of research, high level evidence in the form of randomised controlled trial (RCT) data is only present for compression and for early superficial venous ablation. For the vast majority of other interventions, the existing evidence has been described by Cochrane reviews as *'low quality'*, *'high risk of bias'* and *'in need of further evidence'*. Even in the context of recent evidence and optimal management, as provided by the NIHR funded EVRA trial, healing and recurrence rates are not satisfactory (85.6% healing rate at 24 weeks, 34.6% recurrence at 4 years)(5,9). The COVID-19 pandemic has presented a further challenge, with a drastic reduction in tissue viability services and access to intervention(10,11), resulting in VLU patients being denied treatment or suffering extensive delays in their management. The lessons from the pandemic have generated the need to explore alternative management avenues, including a greater focus on self-management and self-efficacy(12). Platform studies have the advantage of an infrastructure that can evaluate numerous interventions in a more efficient manner than individual RCTs. Our group has extensive experience in delivering NIHR-funded trials and recognises the challenges that large trials present; VLU research lends itself well to a platform approach considering the multiple possible interventions needing assessment (Figure 1).

AIMS

The aim of the study is to develop the optimal design and pathway for versatile and patient-centred research delivery via a future platform study assessing the clinical and cost-effectiveness of intervention for VLU healing and recurrence prevention. The study will be delivered via 5 key work streams (WS):

- WS 1 – evidence synthesis, identification of research priority areas and potential PICO
- WS 2 – establishment of the key study members
- WS 3 – identification of key performance indicators, core outcomes and infrastructure required
- WS 4 – consensus on the optimal design, methodology and delivery of the research
- WS 5 – submission of a platform trial funding application

RESEARCH PLAN AND METHODS

The proposed project will use a mixed methods approach (qualitative and quantitative methodology). The WSs have been developed by all co-applicants, including lay members, members of the collaborating CTUs and health economists. Input was sourced by the pre-award patient and public involvement work, particularly with respect to possible outcomes, feasibility, and platform development group representation.

WS 1 – evidence synthesis and identification of research priority areas (pre award)

A systematic synthesis of the evidence pertaining to VLU healing and prevention will be performed to establish completed and ongoing trials (RCTs) in VLU. This will start upon confirmation of funding and will be led by a project manager (in post, Heatley). Dr Heatley is an experienced trial manager who managed

the NIHR funded EVRA trial and has extensive expertise in VLU RCTs. The evidence synthesis will be performed by two clinical research fellows (in post) following PROSPERO registration and using established databases (EMBASE, MEDLINE, Cochrane database, clinicaltrials.gov amongst others) to identify studies relevant to VLU patients in the following PICO domains:

- Interventions in VLU patient care → to inform possible platform trial arms (including pharmacological, topical and interventional; Figure 1)
- Comparators in VLU trials → to inform the definition of the platform control group
- Outcomes in VLU trials → to inform possible outcomes of the platform trial

A meta-analysis will be performed by the research fellows with support from co-applicants (Onida, Saratzsis, Bown) with expertise and training in this area. The results will be presented and published in scientific journals and patient/clinician friendly documents will be developed summarising the information. It is envisaged that the search strategy will be employed for future reviews to periodically identify novel treatments that can be included as trial arms in the future platform study.

WS 2 – establishment of the platform development group (PDG) (pre award) *(Figure 2)*

Core patient group (CPG): This will be a group of patients, carers and family members (n ~ 10) who will be the voice of VLU patients and will have active input throughout the study period, including in aspects such as: research question priority based on WS1, who they feel should be involved in the platform infrastructure (e.g. patients, allied health professionals); acceptability of study design and treatment; generation and review of patient facing information and research outputs. It is important that the CPG is representative and inclusive. We will adhere to NIHR-INVOLVE, INCLUDE and REPAG principles to maximise minority group recruitment and will use different approaches, including advertising in the national press and social media (Facebook, Twitter, Instagram). Should we not achieve minority group representation, we will ensure lay members are recruited to help identify cultural and/or religious barriers to research participation.

Core clinical group: Clinicians with expertise in VLU management will be recruited to this group (n ~ 10). We performed a consultation exercise in preparation for this application to help inform the composition of this group. This will mirror the feedback received, with ~10 representatives from nursing, vascular surgery, dermatology, interventional radiology, appliance, physiotherapy, pharmacy and general practice. This group will provide clinical and practical expertise to support platform development, provide peer review on possible trial arms to be tested in the future study and comment on the acceptability of new technology (equipoise) They will provide input on clinician dissemination materials to avoid readership burden.

Core stakeholders: Representatives from industry, statisticians, health economists and other additional stakeholders committed to platform development who will meet regularly to advance platform planning. The Core group will undergo platform trial methodology(13) and equality and diversity(14) training.

Specialist Advisory Groups (SPAGs): Additional stakeholders who advise the core groups on platform development via surveys, questionnaires and focussed interviews, where appropriate.

Patient representatives: In addition to the CPG, who will be heavily involved in platform development, individuals interested in contributing to the platform will be involved by completing questionnaires, undertaking focussed interviews, where appropriate, and providing anonymised feedback via a website interface, where preferable. This group will include patients, carers and their family members wishing to provide input into VLU research without committing to be part of the CPG, increasing the depth and breadth of patient feedback on the developing platform study.

Clinical representatives: This group will include representation of national and international societies championing VLU care and research, such as the European College of Phlebology, International Union of Phlebology, American Venous Forum, American Vein and Lymphatic Society, Vascular Society Special Interest Groups, National Wound Care Strategy Programme and Legs Matter. Representatives of the aforementioned bodies have already been contacted and are supportive of this research.

Industry: Industry partners will be invited to participate in the PDG to support the introduction of medical devices and / or pharmacological agents in the trial arms as per pre-application questionnaire feedback.

Statistical expertise: We recognise the challenges in setting up and delivering platform trials. Hence, three established clinical trial units (CTU) will be collaborating on the project, including Imperial, Edinburgh and Leicester CTUs.

Health economics: This will be required to determine the cost effectiveness of different potential interventions. Experts from the University of Granada (Epstein) and the University of Edinburgh (Stoddart), who have collaborated on large RCTs delivered by our group, will be part of the PMG.

Qualitative expertise: Qualitative methodology will feature heavily during platform development. WS 3-6 will rely on focus groups and structured interviews to help establish trial characteristics. Qualitative experts and behavioural health psychologists will join all meetings (Bolton-Saghdaoui, Vedhara, Withers, supported by

Waring) to identify themes and categories to ensure the maximum amount of data can be distilled from group encounters.

Trainee collaboratives: To promote trainee involvement in VLU research and aid delivery of the platform trial, trainee collaboratives will be invited to participate, such as the Vascular and Endovascular Research Network (VERN). The Joint Lead Applicant is a VERN member (Onida). Trainee collaboratives will help comment on feasibility and provide avenues to boost recruitment.

Data science: Evidence based health informatics (EBHI) is increasingly important in evidence appraisal and clinical trial methodology and delivery(15). It is expected that the platform study will generate large volumes of complex data, likely from different centres and countries. In addition, evidence appraisal will need to be integrated to ensure novel treatment modalities can be identified from the literature and incorporated in an efficient manner. Data analytical expertise will be sourced from the BHF Consortium (Onida, Davies, Salim) and the Big Data Analytical Unit (BDAU) at Imperial College. These will help advise the optimal approach for data collection, management and analysis in a centralised, efficient and cost-effective fashion.

WS3 – key performance indicators (KPIs) and characteristics for the platform trial (3 months)

The team members identified in WS2 will participate in interviews, questionnaires and focus groups that will be assessed by experts in qualitative methodology (Bolton-Saghdaoui, Vedhara, Withers supported by Waring) to generate points for discussion in individual focus groups. These may include, among others:

- study design (qualitative vs quantitative approaches, protocol and standardised trial procedure development, integration of trainee collaboratives)
- patient centric methodology (participant identification, treatment identification, screening mechanisms, definition of the control group, definition of core outcome set)(16)
- governance (platform related [centralised data collection, data sharing, data access, information systems] and trial related [comprehensive ethical approval to allow addition and drop out trial arms]
- health economic and statistical methodology (data collection, cost-effectiveness design, pre-trial simulations, power, feasibility, considerations around trial feasibility, interim evaluation frequency, decision rules to add or drop interventions, recruitment challenges, validity of the control group over time, interim analyses timing, platform steering committee meeting timings, recruitment challenges)
- data analytics (integration with registry data to provide contemporary data on existing and emerging technologies; integration with contemporary data to provide information on the population (HES, CPRD, DigiTrials); consideration regarding the possible integration with biobank and biomarker data to explore potential diagnostic and prognostic factors that may be relevant in care personalisation)(17). Contemporary, longitudinal data will be key in enabling the platform to monitor features such as progression of chronic venous disease to ulceration and ulcer recurrence.
- dissemination plans (ensuring data is accessible to all, information understandable by lay individuals and clinicians, consideration of sharing platforms, avoidance of information overload).
- equality and diversity (see next section).

WS4 – consensus on the optimal design, methodology and delivery of the research

Based on WS1-3 data, generation of a PICO framework (Patients, Intervention, Comparator, Outcome) for the platform trial via a Delphi Consensus. During this work stream, which will be informed by the PDG and representatives of the three CTUs, the practical implications of study delivery will be discussed in greater detail. This may include finalising KPIs to assess research delivery and milestones, establish how patients will be identified and approached efficiently based on unique regional and national characteristics, identify success and failure criteria for each intervention relating to safety, considerations regarding recruitment challenges (Jepson), clinical and cost effectiveness, gather consensus (patient and stakeholder) regarding enablers and barriers of delivering the research within predicted timelines and budget, create a vehicle for efficient and timely dissemination throughout trial delivery.

Methodologists from the 3 involved CTUs will liaise to create and model a statistical analysis plan, taking outputs from the previous work streams into account. Once a finalised PICO design has been established, a simulation-based approach will be utilised to investigate and optimise the trial design. The simulations will explore design parameters (such as the thresholds used to determine futility, efficacy and/or cost-effectiveness), and their impact on the platform's type I and II error rate under a range of outcome scenarios. We will also consider factors such as multiple testing adjustment approaches required and discuss how existing national registries or cohort studies can be used to streamline trial delivery.

WS5 – finalising the funding application

Based on WS1-4, a platform trial HTA application will be finalised for the November 2023 deadline. This will be circulated among WS2 members, particularly the CPG to ensure that the proposed research addresses patient wishes and expectations and is acceptable to patients, carers and family members. A formal equality and impact assessment will be performed to identify any risks of under-represented group

exclusion. The proposal will be sent to 5 external reviewers (PPI, Clinician, Methodologist, Statistician and Health Economist) for comments from individuals who have not been involved in the development process to critique it prior to submission.

DESIGN AND THEORETICAL FRAMEWORK FOR WORK STREAMS 2-5

The study will employ a mixed methods approach, including evidence synthesis, interviews, questionnaires, focus groups, Delphi consensus, statistical simulation, and cost-effectiveness model scoping and simulation. Qualitative data will be sourced (minuted) from interviews, focus groups and free text analysis from questionnaires to help inform the WS, with thematic analysis employed to summarise the findings. Team members with expertise in qualitative research (Bolton-Saghdaoui, Vedhara, Withers) will employ a mapping approach to distil the information from the qualitative data. This will be formatted in patient and clinician friendly formats to be regularly delivered to the PDG and updated on the study website.

SAMPLING AND PATIENT AND PUBLIC INVOLVEMENT

The study has been devised with patients at the core. The proposal of a VLU specific platform study was made following the James Lind Alliance prioritisation exercise, which featured VLU research priorities highly across different special interest groups(7,8). The future platform will be able to deliver trials examining these priorities for patient benefit. We have ensured patient and carer representation mirrors clinical representation in the PDG. Participants will be recruited in clinic, online via social media (Facebook, Twitter, Instagram) and with adverts in the national press. It is expected that this will allow interested individuals from different ages and backgrounds to volunteer their participation. The core clinician group will be formed by ~10 representatives based on the pre-application questionnaires (see WS2).

General PPI involvement will be sourced throughout the study period via a dedicated platform website. This will be updated regularly with WS outcomes and will be publicised on social media inviting interested individuals to participate in the research should they wish to. There will also be the option of providing anonymised feedback on the platform, where preferable.

Expert stakeholders, including members of national and international societies, will actively contribute to the platform by participating in questionnaires and focussed interviews. We have strong established links with international phlebological societies; many of these provided input in the pre-application questionnaire, with over 90% stating they would be happy to support the platform study, 89.5% would consider submitting proposals to test via the platform and 100% would support enrolling their patients to participate.

EQUALITY, DIVERSITY AND INCLUSION FOR STUDY PARTICIPANTS

One of the criticisms of large RCTs is their generalisability, with recruited patients often only a small proportion of the screened population and participant ethnicity often skewed. This is true of VLU research; in the EVRA trial, only 7% of the screened population was recruited and over 92% of those recruited were described as white(5). Overall, there is limited representation of ethnic minority groups in VLU research. The representation of other minority groups (religion, sexual orientation) is unknown.

It is important to the study group that the research proposed is generalisable, applicable and inclusive for all patients, particularly under-served groups. To ensure this, we will take the following measures:

1. Recruitment of patients from different backgrounds to the core patient group as per NIHR-INCLUDE and REPAG guidelines, paying particular attention to the Equality, Diversity and Inclusion (EDI) NIHR groups. This will ensure that the platform will be designed with underserved groups in mind. Should there be paucity of under-represented group members, we will invite representatives to sit on the core patient group. One of our patient co-Applicants is a minority group representative.
2. Equality and diversity training for the core platform members(14)
3. Equality and Diversity focus group – there will be a dedicated focus group on this topic as part of the platform trial development in WS3. The information from this will be included in WS4-5.
4. Ensuring that the language used in documents is inclusive and understandable (developed by the CPG)
5. Performing and Equality Impact Assessment (EIA) as part of WS4-5 to ensure equality and diversity considerations have been formally assessed based on the treatments that will be included in the future platform trial application. If any are identified, making a clear plan to address them.
6. Develop the trial according to the INCLUDE Ethnicity Framework(18) addressing the four key questions and following the INCLUDE roadmap.

DATA COLLECTION AND DATA ANALYSIS

Interviews, focus groups, meetings and the free text content of questionnaire responses will be analysed by thematic analysis using a mapping approach by team members with expertise in qualitative research (Bolton-Saghdaoui, Vedhara, Withers, Waring). The statistical analytical details will be finalised by the three CTUs during the platform development, including integration of large dataset analytics based on the results of WS3-4. Complex simulations will be carried out to develop and optimise platform trial design.

COST EFFECTIVENESS ANALYSIS

The cost effectiveness analytical plan will be developed as part of WS3 and 4. Two experienced health economist are part of the study team and will provide information on data points for collection based on the treatment modalities that will be assessed. This will include the development of a schematic for a core structure for an economic model which can be adapted for use with a variety of interventions for VLU, with key health states based on outcomes of interest identified by WS1-4. While other model structures will be considered, it is anticipated that this will take the form of a Markov model with base case analysis derived from NICE reference case specifications(19), with optional additional inputs for non-NHS/PSS costs and outcomes identified in the consultation exercises as needed. The model will be adapted according to the progression of the trial, with its corresponding estimates of uncertainty used to inform decisions about adding or removing interventions, alongside other aspects of the adaptive platform design.

DISSEMINATION, OUTPUTS AND ANTICIPATED IMPACT

What do you intend to produce from your research?

1. A summary of the evidence for all types VLU intervention and a finalised list of possible interventions to be assessed by the platform; this will be published in a peer reviewed paper
2. A PDG composed of patients, clinicians, key stakeholders and national/international collaborators
3. The definitions of the KPIs and platform trial characteristics for VLU research
4. The infrastructure of the platform (database, data analytics components) to streamline platform activities
5. The details of the proposed platform trial in VLU with a peer-reviewed funding application to be submitted to the NIHR in November 2023
6. A mechanism by which existing registries, primary and secondary care databases and cohort studies can be interlinked to help support data collection for the platform trial
7. A mechanism by which new treatments can be identified in the literature and added as platform arms
8. A mechanism by which interactions between different interventions can be assessed
9. Success and failure criteria for interventions relating to safety, clinical and cost effectiveness
10. An outline of the health economic model to be used in the platform trial
11. A vehicle for efficient and timely international dissemination for vascular trials
12. A list of national and international collaborators to support the future trial
13. A publication summarising the proposed platform trial methodology, following Guidance for Reporting Involvement of Patients and Public (GRIPP) guidelines with respect to PPI involvement(20).

How will you inform and engage the wider population?

The study website will be publicised regularly via different social media interfaces. We will develop patient friendly videos to help describe the study outcomes and how the platform development is progressing, inviting feedback from the wider VLU population. These will be disseminated via national patient groups (Legs Matter, Lindsey Leg Club, James Lind Alliance), the Vascular Research UK website, YouTube Channel, social media and to nursing/community care groups, including clinical research nurse networks.

WHAT FURTHER FUNDING OR SUPPORT WILL BE REQUIRED?

We will submit an application to the 2023 NIHR HTA programme to fund the platform trial.

SUCCESS CRITERIA AND BARRIERS FOR FURTHER RESEARCH IMPLEMENTATION

Success criteria relate to the delivery of the WS according to planned activities (see Gantt chart). Core team members will meet on a weekly basis to ensure study progression according to the milestones. Possible barriers and mitigation strategies:

1. Patient involvement – patients with VLU are often elderly and socio-economically deprived. We have adapted interfaces to facilitate trial participation (social media, adverts in the paper, telephone or video or face to face consultations) and provide funding to help facilitate travel for face-to-face meetings where required. One of our co-applicants has expertise in recruitment challenges (Jepson)
2. Under representation of minority groups – we have included training in equality and diversity, have a minority co-applicant representative and will champion minority group representation in the PDG. Where this is not possible, lay minority representatives will be included.
3. Platform trial delivery – this will be the first platform development in VLU. We have included training in platform methodology for the PDG to ensure everyone understands what this is and have selected a group of co-applicants with expertise in VLU trial delivery and strong established collaborative links to help support delivery of the platform.
4. Data management – the future platform study will generate large amounts of data, requiring facilities to manage this and the development of methodology to routinely and efficiently review the existing

literature to help identify possible treatments to add to the platform. We have three expert CTUs supporting the trial and will source advice from data analytics experts (BHF Consortium and BDAU at Imperial) to help manage large datasets.

5. A future platform study will need considerable resources; we will apply for HTA funding for this in 2023.

WHAT DO YOU THINK THE IMPACT OF YOUR RESEARCH WILL BE AND FOR WHOM?

The impact of the future trial will be providing the evidence on which treatments are best placed to support VLU healing and prevent recurrence, resulting in markedly improved health outcomes for this patient group. This evidence can impact upon national and international guidance, improving patient care and reducing the national and international burden of disease. This will have a further impact on the financial and social burden of VLU, resulting in cost savings to the healthcare service.

HOW WILL YOU SHARE THE PROGRESS AND FINDINGS OF YOUR RESEARCH?

We will update the platform website regularly and publicise this on social media, patient and phlebology groups in lay format (written and video). The members of the core patient group will help develop this to avoid readership burden. National and international groups will disseminate findings via their membership.

TIMETABLE – PLEASE SEE GANTT CHART

Setup (3 months). WS1 – 2 months, pre-award. WS2 – 3 months, pre award. WS 3 – 3 months. WS4 – 3 months, WS5 – 3 months.

PROJECT MANAGEMENT AND ETHICS

All staff are already in post, including an experienced project manager (Dr Heatley) and the two Co-Is (Onida and Davies), who together will form the executive group and will facilitate research delivery with PPI and statistical input. Imperial College, NIHR Leicester BRC and Edinburgh, Leicester and Imperial trials units will help support research delivery (Professors Cornelius, Murphy and Norrie). Many of the co-applicants have collaborated in NIHR studies and have strong established links with a track record of research delivery. Ethical approval will be sought as per NIHR, HRA guidance and UK Framework for Health and Social Care Research.

TEAM AND PROJECT / RESEARCH EXPERTISE

Project development: The project has been developed by the Vascular Society Research Committee Chair and BHF Chair in Vascular Surgery (Professor Bown), Venous (Mr Carradice) and Wound (Professor Chetter) Special Interest Groups, in addition to patients, representatives from nursing (Ms Dumville and Ms Atkin), pharmacy (Dr Di Puma), vascular science (Dr Rogers) and other key stakeholders in VLU care. The CI is a NIHR Senior Investigator (Professor Davies) with extensive experience in delivering NIHR-funded projects. The Joint CI (Miss Onida) is an academic vascular surgeon, previous NIHR funded Clinical Lecturer with a major research interest in VLU. The project is supported by the Director of Clinical Research at the Royal College of Surgeons of England (Professor Hutchinson). **Management**: Dr Heatley is already in post and will undertake the day-to-day study management with Miss Onida and Professor Davies. **Methodology:** The team is supported by experienced statisticians and methodologists from three CTUs (Norrie, Cornelius, Murphy, in post) and two experienced health economists (Drs Epstein and Stoddart). Qualitative expertise is provided by Miss Bolton-Saghdaoui (vascular nursing academic with expertise in thematic mapping) Professor Vedhara (behavioural analysis and interventions), Professor Greaves (behavioural interventions) and Dr Withers (work package thematic analysis and intervention-mapping expertise) supported by Professor Waring (world leading expertise in implementation and medical sociology). Dr Salim has expertise in large dataset integration and analysis, has worked with the Imperial BDAU and, with Miss Onida and Professor Davies, is part of the BHF COVID-UK Consortium, with expertise in large dataset analysis. **Implementation**: Professor Pinkney has expertise in delivering NIHR supported complex trials and will advise on trial delivery. Dr Jepson has expertise relating to supporting recruitment to RCTs using qualitative methodology. **Primary care:** Professor Azeem Majeed, Dr David Wingfield and Dr Adarsh Babber will provide public health and primary care input. **PPI:** The two PPI representatives (Ms Gibson and Mr Ezeife) are of different gender and ethnic backgrounds. Both have had longstanding ulceration and have provided PPI support for trials in the past. Both found the REALMS interface challenging to use and were unable to complete co-applicant tasks on the website but are very much VEINS co-applicants and fully supportive of the study. **Additional:** The team also includes experts in deep venous intervention (Professor Black), interventional radiology (Dr Karunanithy), haematology (Dr Breem) and representatives of the Royal Society of Medicine Venous Forum (Mr Gohel), the European College of Phlebology (Professors Wittens, Davies), the American Venous Forum (Dr Marston), the International Union of Phlebology (Dr Parsi), the American Vein and Lymphatic Society (Dr Gibson) and

appliance / industry specialists (Ms Linnitt). All key stakeholders are in post and are participating at no additional cost.

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