Designing a platform trial to assess the effectiveness of treatments for peripheral arterial disease

BACKGROUND AND RATIONALE

Peripheral Arterial Disease (PAD) affects a fifth of people over the age of 55 and its prevalence is steadily increasing(1-3). PAD is the commonest cause of amputation and a leading cause of cardiovascular morbidity worldwide(4). It makes up 75% of current vascular healthcare workload across primary, community, and secondary care. More than half of those with symptomatic PAD are expected to die, have an amputation or cardiovascular event within five years, which has not improved despite advances in care(2, 5-8). People with symptomatic PAD present with intermittent claudication or Chronic Limb Threatening Ischaemia (CLTI) i.e. leg pain at rest or gangrene/ulceration(4). CLTI is limb and life threatening, requiring urgent revascularisation(4). Those with claudication require exercise therapy and occasionally revascularisation to alleviate pain(9). All patients with symptomatic PAD require risk-factor modification and medications to reduce cardiovascular risk and PAD progression. Most revascularisation procedures for PAD are endovascular i.e. minimally invasive. Several new endovascular technologies (e.g. stents and other adjuncts) and medications are regularly introduced in clinical care. The clinical and cost-effectiveness of these interventions, however, is unknown, as they have not been assessed in high-quality randomised studies. The continuous introduction of new PAD technologies and the fact that they can be used contemporaneously, and heterogeneity of presentation of patients with PAD further complicate their assessment. Most PAD technologies and new treatments are used in routine care without adequate scrutiny. This area has been identified as a key research priority in a recent JLA Priority Setting Partnership (PSP) with the Vascular Society of Great Britain and Ireland (VSGBI)(1). Further, patients in focus groups and surveys as part of this application and our ongoing NIHR-funded research are concerned about the lack of evidence to support decision-making when they are offered treatment. Overall, the universal lack of high-quality randomised evidence assessing the effectiveness and long-term results of new PAD technologies and medications is leading to more deaths, amputations, increased healthcare costs, and uncertainty regarding decision-making. This can only be addressed using a platform trial design. An ideal PAD trial should generate evidence rapidly, account for disease heterogeneity and variation in treatment effects, assess multiple potentially interacting treatments concurrently, take patients' views into account and create a durable infrastructure for ongoing evidence generation. We plan to such a platform trial assessing new PAD technologies and medications, which will improve patient care, end treatment uncertainty, and decrease healthcare costs. This will act as a model design to allow delivery of future ambitious trials in other vascular disease areas.

EVIDENCE EXPLAINING WHY THIS RESEARCH IS NEEDED NOW

We performed a systematic search and reviewed all PAD guidelines in September 2022 to identify complex vascular trials, and currently available PAD treatments/medications. We recently published 3 international studies (52 centres, 3,289 patients) investigating new invasive treatments for patients with aorto-iliac or infrainguinal PAD (10-12). We have identified the following:

- Symptomatic PAD is the commonest arterial pathology requiring specialist treatment (13)
- There is variation in PAD medications and types of revascularisation offered to patients(14)
- Modern pharmacotherapies for PAD have not been assessed in high-quality trials
- Most endovascular PAD treatments have not been tested in a randomised trial
- Some new PAD treatments might be associated with increased mortality/amputation risk(15)
- Interactions between endovascular technologies and medications have never been assessed.

Key challenges in delivering a platform trial to address the above issues, include:

- Patients with PAD are usually frail, with multiple co-morbidities, and socio-economically deprived
- Several new interventional and pharmaceutical PAD treatments are made available yearly
- There are no core outcome sets for patients with PAD
- The opinions and views of patients or healthcare professionals have not been explored.

AIMS & OBJECTIVES

Main aim: Identify the optimal design and pathway for research delivery for a large-scale platform RCT assessing the clinical and cost-effectiveness of interventions for patients with symptomatic PAD. The **objectives per work package** are listed below.

Work package 1 - evidence synthesis to identify:

- Ongoing and completed complex RCTs relating to any cardiovascular disease
- Interventions to be assessed in the future platform trial (both interventional and pharmaceutical)
- Comparators
- Outcomes of interest, including relevant health states for economic modelling.

Work package 2 - **set up lay and expert groups to guide research design**

- Use our existing PAD lay groups to set up a new project-specific patient and public involvement panel
- Institute an international group of professional stakeholders to lead trial design

Work package 3 - define the trial's **ideal characteristics** & key performance indicators (**KPIs**) regarding:

- Screening, randomisation, and treatment allocation mechanisms
- Requirements needed to be met before an intervention is deemed appropriate to enter the trial
- Outcome assessments, treatment delivery assessment per arm, health economic data collection
- Cost-effective design and model structure, sustainability, and longevity, including use of existing resources (e.g. routinely collected data, existing cohort studies, National Vascular Registry integration)
- Implementation research and qualitative appraisal within the trial

Work package 4 - gain **consensus** to design the research

- Finalise the PICO design of the ideal PAD platform trial
- Finalise KPIs to assess patient safety, research delivery success, and milestones
- Create a blueprint for collaboration between existing vascular registries, trials, and cohort studies in the NHS and abroad to establish recruitment and patient follow-up strategies
- Establish a mechanism via which arms will be added or removed in the platform trial
- Identify how interactions between different treatments will be assessed
- Create a vehicle for efficient and timely international dissemination alongside trial delivery.
- Consensus on appropriate core structure for economic modelling

Work package 5 - finalise the trial protocol and funding application.

RESEARCH PLAN AND METHODS

A mixed methods approach will be used in 5 work packages. The format and duration of each package were proposed by our lay co-applicants. Qualitative data from our NIHR CHABLIS study (ISRCTN13202085) investigating barriers and enablers to provision of PAD treatments were used. We interviewed 120 patients with PAD to understand different pathways of treatment, barriers to medical therapy and receiving intervention. The work packages were subsequently developed based on this information during weekly meetings involving methodologists from 3 CTUs (Edinburgh, Imperial, Leicester), the lay co-applicants, Vascular Society of Great Britain and Ireland (VSGBI), Royal College of Surgeons (England), British Society or Interventional Radiology (BSIR), Research Collaborative for PAD (RCPAD, 17 vascular European centres), Vascular and Endovascular Research Network (VERN, 53 countries), and British Society for Endovascular Therapy (BSET).

Work package 1 - evidence synthesis to inform subsequent study design

The 1st work package will be led by researchers with evidence-synthesis expertise (Carradice, Saratzis, Bown, Normahani) and build on our ongoing NIHR RfPB evidence-synthesis work in PAD, led by Mr Carradice (co-applicant). MEDLINE, EMBASE, clinicaltrials.gov, WHO Trials Database. and ISRCTN will be searched to identify ongoing and completed complex cardiovascular trials, PAD-specific interventions to be assessed in the future trial, comparators and outcomes of interest, including key health states to be simulated in health economic modelling. A summation analysis will be performed; patient and clinician friendly documents will be developed summarising all available information. **Outputs from WP1: Lists** of pharmaceutical, non-invasive, and invasive technologies for PAD with a summary of the available evidence per treatment in expert/lay format. An established **adaptive PAD-specific search strategy** to ensure new treatments can be identified and added to the future trial whilst it is recruiting.

Work package 2 - setting up lay and expert groups to guide study design

Lay groups: We will recruit to a new project-specific PPI panel (8 members) based on the PROGRESS-Plus guidance, to ensure representation from groups more likely to suffer with PAD. They will act as the

main vehicle for PPI alongside our 2 co-applicants. Recruitment will take place via our PAD groups in Leicester and London, social media (project-specific Facebook, Twitter, Instagram pages), a website, the JLA, u3a, and Self Help UK. Participants will receive training regarding mixed methods research (costed). **Expert groups:** We will institute an international group of professional stakeholders (minimum 10 participants) across specialties. Industry partners from companies which manufacture PAD products and therapies have already agreed to take part (8 companies). To ensure broad representation we will advertise the project via the Society for Vascular Nursing, Society for Vascular Technology, physiotherapy, podiatry, pharmacy, and vascular networks internationally. **Outputs from WP2: lay/expert/industry groups for this project and the future platform trial.**

Work package 3 - define characteristics & key performance indicators (KPIs) of a PAD platform trial

A one-day lay and expert workshop will be held (members identified in WP2). Summaries from WP1 will be sent to participants beforehand (lay/expert format). The event will be recorded and minuted by a researcher with expertise in co-creation (Withers) and the project manager. Minutes/recording will be analysed (thematic analysis) to draw out the **WP3 outputs**: **list** of **ideal future trial characteristics** and **KPIs**.

Work package 4 - gain consensus to design the future research protocol

Outputs from WP1 and WP3 will be taken into a modified Delphi process involving lay and expert participants, to reach consensus regarding all 6 objectives of work package 4 (final characteristics and design of the future platform trial). The Delphi will be held using a hybrid format to facilitate patient and expert participation both online and via interviews. We will use the same Delphi process which we piloted in the CRISP NIHR Advanced Fellowship (Saratzis), and NIHR RfPB CHABLIS study, involving patients with PAD. Further, methodologists from the 3 CTUs will create and model a statistical analysis plan, taking outputs from the previous packages into account. We will also finalise a plan regarding how existing registries and datasets (e.g. the National Vascular Registry which collects data on all PAD interventions across the UK) or studies can be used to streamline trial delivery. **WP4 outputs**: **consensus on key characteristics of the future platform trial protocol** and **draft trial design**.

Work package 5 - finalise the trial protocol and funding application

Outputs from all packages and the WP4 draft will be used to finalise the protocol and application to NIHR HTA, including a protocol and statistical analysis plan. Over a one month period the text will be circulated amongst the research team for feedback. The application will be submitted in November 2023. Once NIHR feedback has been received, we will convene a meeting with lay and expert partners to finalise the Stage 2 application (consensus conference).

The attached **flowchart** and CTU work **logic model** summarise work packages, outputs, and project flow.

DESIGN AND THEORETICAL FRAMEWORK FOR PACKAGES 2 - 5

We will host workshops, focus groups, and a final consensus conference, facilitated by online surveys and a study-specific website. All meetings will be attended by an expert in co-creation and intervention mapping (Withers) and will be facilitated by the project manager. PPI engagement will be sustained via traditional approaches (workshops, focus groups) and online participation (surveys, project-specific interactive website, social media groups). We will produce summaries and mind maps of points discussed at each meeting in lay and expert language. Thematic analysis will be used to analyse recordings/minutes. We will draw on theory on innovation management and implementation science to understand the innovation landscape for PAD and consider the factors shaping development, testing, implementation and normalisation of interventions across different organisational contexts.

SAMPLING

PPI: Participants will be recruited from our PAD-specific PPI groups. Further, participants will be recruited online, via social media (mostly Facebook), and purposefully via interaction with certain ethnic minorities or social groups**.** In our previous NIHR research relating to PAD or CLTI we have already established strong PPI links with community leaders amongst ethnic minorities who are more likely to have PAD and key patient groups across the country. **Expert stakeholders:** We will use established networks to approach

healthcare professionals from all relevant PAD backgrounds internationally. The future platform trial will recruit all patients with symptomatic PAD who receive treatment in primary or secondary care. The exact nature, funding, and pathway of involvement from international sites will be finalised during this project.

EQUALITY, DIVERSITY AND INCLUSION FOR STUDY PARTICIPANTS

Attention has been paid to ensuring inclusion of all potential participants via the following strategies:

- No upper age, sex, gender, disability or social construct restriction for recruitment. All adult patients with PAD, their carers, and families will be eligible for inclusion. Healthcare professionals from any background as well as industry (pharmaceutical) representatives will be eligible to take part.
- Adhering to the Trial Forge Include Ethnicity framework; results will apply to all community groups since there is no restriction on participation. Materials will be available in common languages and representing ethnic groups known to have a higher prevalence of PAD
- We will promote the research via several different avenues and media and purposefully sample PPI participants with diverse backgrounds, amongst ethnic minorities (e.g. Asian) known to have a higher prevalence of PAD or diabetes, and socioeconomically deprived areas, including the 5 NHS regions with the higher prevalence of amputations due to PAD. For patients with mobility or other issues who cannot take part in face to face workshops, we will offer the option of interviews, including interview with the support of a translator. The patient will be able to choose the location, time and whether the interview takes place online, over the phone or face to face.
- The research team is diverse and includes representatives across disciplines, with PPI partners from diverse ethnic and socioeconomic backgrounds.
- A strong equality, diversity, and inclusion package will be embedded in our protocol for the future trial.

DATA COLLECTION & DATA ANALYSIS

Workshops, focus groups, interviews will be recorded/minuted. Findings will be summarised with thematic analysis. A mapping approach will be used for each workshop by a behavioural scientist with expertise in intervention mapping, will lead this, supported by Professor Waring, with world-class expertise in implementation and medical sociology. The statistical analysis plan of the proposed trial will be finalised by statisticians and methodologists from 3 CTUs as part of Work Package 4 using outputs from all the packages. The statisticians will used a modelling approach to ensure that the statistical analysis plan for the final proposal is appropriate and scalable.

MEASUREMENT OF COSTS AND OUTCOMES - HEALTH ECONOMIC ASSESSMENT

A plan for a health economic sub-study will be designed alongside the wider protocol. 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 PAD, 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(16), with optional additional inputs for non NHS/ personal social services costs and outcomes identified in the consultation exercises as needed. Analyses will be adapted according to the progression of the trial, based on predefined success and failure criteria, likely incorporating value of information analysis. The model and estimates of uncertainty will be used to inform decisions about adding/removing interventions. Two experienced Health Economists (Stoddart, Epstein) will support our project and design this plan.

DISSEMINATION, OUTPUTS, AND ANTICIPATED IMPACT

What do you intend to produce from your research?

1) Latest available **evidence** regarding: Ongoing and completed complex RCTs in patients with cardiovascular diseases; Interventions to be assessed; Comparators; Outcomes of interest.
2) A lay and an expert **disease-specific group** to plan complex trials in PAD
3) Definitions of the ideal characteristics and KPIs of a platform trial in PAD
4) A mature trial design and protocol for a platform trial in PAD
5) A blueprint for collaboration between existing vascular registries, trials and cohort studies internationally, to streamline efficient recruitment and patient follow-up in vascular trials

6) A mechanism via which new technologies will be added to PAD platform trials in the future
7) A mechanism via which interactions between different PAD treatments can be assessed
8) Success and failure criteria for PAD interventions relating to safety, clinical, and cost-effectiveness
9) A core structure for an economic model to be used for interventions utilising the platform.
10) A vehicle for efficient and timely international dissemination for complex PAD trials.

How will you inform and engage the wider population?

We involved healthcare professionals via the Vascular Society PAD group (Saratzis, Coughlin), which includes members from all disciplines involved in PAD care. Our strategy of publishing outputs in lay and expert format on a trial-specific website, social media, and directly communicating these to NHS and vascular healthcare societies, will ensure the widest possible reach. Patient support groups such as the JLA or Self Help UK will be given lay summaries regularly and disseminate accordingly.

WHAT FURTHER FUNDING OR SUPPORT WILL BE REQUIRED?

We will apply to the NIHR HTA Programme in 2023 to fund the developed PAD platform trial.

SUCCESS CRITERIA & BARRIERS FOR FURTHER RESEARCH AND IMPLEMENTATION

Success criteria relate to the delivery of the planned activities on time and cost. A weekly team meeting will ensure that we deliver each work package as per the attached Gantt chart/flowchart.
Potential barriers and mitigation strategies include:

- Patients with PAD are frail, suffer with multiple co-morbidities, and are typically socio-economically deprived. Their participation in complex research projects will require specific support and tailored recruitment practices. We have a thorough support package for PPI interaction factored in our design.
- There have been no previous platform trials in this clinical area. Our project will define key characteristics and performance indicators of a platform PAD trial
- Several new interventional and pharmaceutical treatments are made available for this patient group yearly. Our project will define how we will select new treatments to ensure the longevity of the platform trial, following our initial systematic review (work package 1)
- There are no core outcome sets in PAD. We will use extensive PPI interaction to define appropriate outcomes for the duration of the study, both for those with claudication and those with CLTI.

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

Patient/service user benefit & public wellbeing: The immediate impact of the future trial will be the provision of definitive evidence regarding the cost and clinical effectiveness of PAD treatments. This will end treatment uncertainty regarding the choice of treatment for PAD and benefit patients by preventing deaths/amputations. Even a modest reduction of mortality and major morbidity by 10% when treating patients with PAD in the NHS will save 7,000 lives and legs and £180 million per year. **Changes in care:** The future trial has the potential to impact on the type of interventions or pharmaceutical treatments offered to those with PAD. This will impact on the type of PAD treatments in the NHS and worldwide. This work will be a paradigm for future vascular trials.

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

Participants (experts/lay), the Vascular Research Network, JLA, and Self Help UK will receive personal communications with updates digitally and in print. We will use social media and a project website to link to lay updates prepared by our PPI partners. International societies (already partners in this project) will disseminate findings via direct communications to their membership.

TIMETABLE - A Gantt chart is attached

Set-up: 2 months for approvals/set up. **Work package 1:** 2 months, **Work package 2**: 1 month, **Work packages 3 & 4**: 3 months, including 2 days for focus groups, workshops, and 2 months for analysis and dissemination. **Work package 5:** Draft initial proposal/research plan: 1 month, followed by a round of

feedback from lay and expert partners, before submission to NIHR in November 2023. Following receipt of feedback from Stage 1, a month will be dedicated to revise and submit the Stage 2 application HTA.

PROJECT MANAGEMENT AND ETHICS

All staff are already in post. An experienced project manager has been costed (in post - Imperial College). They will facilitate delivery of the project with the support of the two coCIs (Saratzis, Davies). A weekly meeting will be held given the complexities of delivering this project. Imperial College, NIHR Leicester BRC, the two CIs and the involved CTUs already deliver a number of NIHR PAD projects and will use existing collaborations to deliver this project on time. Regulatory approvals will be sought as per NIHR, HRA guidance and UK Framework for Health and Social Care Research.

TEAM AND PROJECT / RESEARCH EXPERTISE

The project has been developed by the membership of the VSGBI PAD specialist interest group including all professions that deliver PAD care. Mr Saratzis (CI) is an NIHR Advanced Fellow, member of an NIHR HTA Committee, various PAD panels, with experience in leading NIHR-funded projects (PGfAR, RfPB, HTA, HS&DR). He will be supported by an NIHR Senior Investigator (Davies, Imperial College), 3 CTUs, the Director of Clinical Research at the Royal College of Surgeons of England (Hutchinson), VSGBI Research Lead and BHF Chair of Vascular Surgery (Bown). A dedicated project manager and statisticians/methodologists with complex trial expertise will contribute (all in post). The core team is leading a considerable portfolio of NIHR research relating to PAD, including 5 HTA trials. There is some overlap of co-applicants with surgical expertise between 3 development bids/applications (NIHR 155342, 156728, 155477) to this commissioned call (please see **letter** by Professors Pinkney and Hutchinson). This enables the appropriate delivery of methodological and clinical expertise for the 3 bids without a negative impact on the applications or potential future studies – more it demonstrates the willingness of our networks to work constructively together to create/deliver these long-needed complex surgical trials to benefit patients.

Methodology expertise: Professor Waring (Professor of Medical Sociology and Healthcare Organisation) will provide expertise on healthcare systems' delivery, qualitative research, and implementation. Professor Pinkney [Director of the Birmingham Surgical Trials Consortium (BiSTC) and the Birmingham Centre for Observational and Prospective Studies (BiCOPS)] will advise on trial-delivery mechanisms, given his experience delivering complex NIHR funded surgical trials. Dr Withers (Psychologist) will support the thematic analysis of the work packages and brings intervention-mapping expertise, which will be used to develop the final application/trial-design. Senior world-class methodologists from all 3 CTUs will support the statistical analysis plan development and model the future trial. Two senior Health Economists will support the relevant elements of the project (Stoddart, Epstein). Mr Carradice holds an NIHR RfPB award relating to a meta-analysis regarding medical PAD treatments and will support WP1 (literature synthesis). Public Health and Primary care experts include Dr David Wingfield and Professor Azeem Majeed, who will ensure the developed trial reflects current NHS care pathways. A team of 10 independent experts will review the Stage 1 application externally prior to submission, with the support of East Midlands NIHR RDS.

PPI expertise: Our 2 PPI co-applicants have had CLTI (severe PAD) and will be liaising with our separate PPI group regularly. They have experience of both medical and surgical/endovascular treatment(s) for PAD in the NHS (England and Scotland) and will receive further training in trials and the disease area (costed).

Specialist clinical expertise: Our team represents the whole spectrum of PAD healthcare provision, including a vascular nurse co-applicant with expertise in PAD (Ashton); Professor Gavin Murphy (BHF Chair in Cardiac Surgery, Leicester CTU lead); representatives from the National Vascular Registry/VSGBI (Chetter, Bown, Smith, Carradice), international Research Collaborative for PAD (RCPAD; Saratzis, Zayed, Stavroulakis), British Society for Interventional Radiology (Hamady, Diamantopoulos), European Society for Vascular Surgery (Van Herzeele), Royal College of Surgeons of England (Hutchinson), British Society for Endovascular Therapy (Bicknell, Bosanquet), and Society for Vascular Technology (Rogers).

Industry representation: We secured industry representatives' participation to all workshops and work packages (14 individuals from 8 endovascular and 4 pharmaceutical companies) at no additional cost. Mr Saratzis and Mr Bicknell will liaise with industry experts to ensure broad and independent representation.