**Full Study Title:** A Community and Hospital cAre Bundle to improve the medical treatment of cLaudIcation and critical limb iSchaemia (CHABLIS).

**Short Title:** The CHABLIS study.

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| Signatures: | The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol |

Confidentiality Statement

All information contained within this protocol is regarded as, and must be kept confidential.  No part of it may be disclosed by any Receiving Party to any Third Party, at any time, or in any form without the express written permission from the Chief Author/Investigator and the Sponsor (University of Leicester).

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# AMENDMENT HISTORY

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| **Amendment No.** | **Protocol Version No.** | **Date issued** | **Author(s) of changes** | **Details of Changes made** |
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# SYNOPSIS

|  |  |
| --- | --- |
| **Study Title** | A Community and Hospital cAre Bundle to improve the medical treatment of cLaudIcation and critical limb iSchaemia (CHABLIS). |
| **Study Design** | Prospective feasibility multicentre cohort study |
| **Participants** | Adult patients with symptomatic Peripheral Arterial Disease (PAD) referred to secondary care, either in a clinic or for inpatient treatment. |
| **Planned Sample Size** | 186 patients (recruited) – 93 patients completing follow-up. |
| **Follow-up duration** | Six (6) months. |
| **Planned Study Period** | Start date: 01/11/2020 (1st November 2020)  Set-up: Six months  Recruitment: Six months  Follow-up: Six months  Analyses: Four months  Consensus conference: One-day event on completion of analyses  Full dissemination: Two months after the consensus conference. |
| **Primary Aim and Primary Objective** | The main **aim** of this research is to assess whether the LEGS intervention can be used in the routine care of patients who present with symptomatic PAD (i.e. Intermittent Claudication or Chronic Limb Threatening Ischaemia). We will therefore assess the fidelity of delivering the intervention and acceptability by patients and stakeholders.  The primary **objective** is to assess the fidelity of delivering the LEGS intervention in existing NHS care pathways and acceptability of each intervention component by patients and stakeholders. |
| **Secondary Aim(s)**  **and Secondary Objective(s)** | This feasibility study will also produce qualitative data which will allow us to adapt the intervention to NHS care pathways and quantitative data that will inform future research assessing clinical and cost effectiveness. |
| **Primary Endpoint/Outcome Measure** | Fidelity of intervention delivery (assessed quantitatively regarding adherence and qualitatively regarding overall impression/acceptability). |
| **Secondary Endpoints/Outcome Measures** | Proportion of patients agreeing to take part out of all patients invited (intervention recruitment rate)  Proportion of patients recruited who provide data at the end of the study period (intervention retention rate). |

# ABBREVIATIONS

AE Adverse event

AR Adverse reaction

CI Chief Investigator

CLTI Chronic Limb Threatening Ischaemia

CRA Clinical Research Associate (Monitor)

CRF Case Report Form

CT Clinical Trials

EC Ethics Committee (see REC)

GCP Good Clinical Practice

GP General Practitioner

IC Intermittent Claudication

ICF Informed Consent Form

LEGS LEaflet Gp letter Structured checklist

NHS National Health Service

NIHR National Institute for Health Research

NRES National Research Ethics Service

PAD Peripheral Arterial Disease or Peripheral Artery Disease

PI Principal Investigator

PPI Patient and Public Involvement

PIL/S Participant/ Patient Information Leaflet/Sheet

R&D NHS Trust R&D Department

REC Research Ethics Committee

SAE Serious Adverse Event

SAR Serious Adverse Reaction

SOP Standard Operating Procedure

SUSAR Suspected Unexpected Serious Adverse Reactions

SMF Study Master File

SSC Study Steering Committee

TMF Trial Master File

UK United Kingdom

# BACKGROUND AND RATIONALE

**What is the problem being addressed?**

Peripheral Arterial Disease (PAD) affects a fifth of people over the age of 60 in the United Kingdom (1-3). It is the commonest cause of limb amputation and a leading cause of cardiovascular morbidity(4). Patients with PAD who develop symptoms present either with intermittent claudication or chronic limb threatening ischaemia. More than half of those diagnosed with symptomatic PAD are expected to die, have an amputation or a major cardiovascular event within five years (2, 5-8). Many of their cardiovascular risk-factors, such as smoking, high blood pressure, hyperlipidaemia, and poor glucose control, are modifiable. Current National Institute for Healthcare Excellence (NICE) guidance sets clear targets regarding how these risk-factors should be addressed to prevent cardiac events and amputations(3). Using national data for patients presenting with symptomatic PAD we calculated that controlling these modifiable risk factors would lead to an absolute risk reduction of their median ten-year cardiovascular risk by 29%, adding six cardiovascular disease-free years to their life expectancy (9).

Our research has shown very poor implementation of NICE PAD guidance in the NHS (9). Only a tenth of patients are prescribed appropriate preventive medication. The vast majority continue to have high blood pressure or smoke and almost none receive structured lifestyle or dietary support (9) after being diagnosed with PAD.

Through interaction with patients, primary and secondary care stakeholders, we identified key barriers in implementing NICE PAD guidance in the NHS: lack of communication between primary and secondary care; poor patient education regarding side effects of medication, need for pharmacotherapy to prevent cardiovascular events, and treatment targets; inconsistent prescription practices in primary and secondary care; lack of awareness of NICE PAD guidance amongst doctors.

To address these, we developed a bundle of documents for use in both primary and secondary care, the “LEGS” (**LE**aflet **G**p letter **S**tructured checklist) intervention. LEGS is based on the needs and perceptions of patients with PAD based on Patient and Public Involvement (PPI) workshops and interviews. To ensure the need of care providers are met, we also consulted primary and secondary care clinicians nationally. LEGS aims to support patients with symptomatic PAD, GPs, and hospital doctors to actively manage modifiable risk-factors with up to date information and easy-to-use checklists. As per the 2019 Medical Research Council (MRC) and NIHR “Developing and Evaluating Complex Interventions” document, we now aim to test whether LEGS can indeed be used in current NHS care pathways.

**Importance of this research.**

PAD presentation and prevalence

Around 20% of people above 60 years have PAD (2, 6-8). The prevalence of PAD is expected to rise, due to a sedentary life-style, poor dietary choices, rising prevalence of diabetes and longer life-expectancy (3, 10, 11). The most common presentation of symptomatic PAD is IC. In some cases the reduction in blood flow is so severe that it causes pain at rest, ulceration or gangrene, which constitute chronic limb threatening ischaemia - the most severe form of PAD. Approximately 5% of individuals between the age of 55 and 74 have intermittent claudication or chronic limb threatening ischaemia (1, 2, 6-8, 11). Patients with intermittent claudication are more likely to suffer cardiovascular events compared to age-matched individuals (5, 6, 12). Of those with IC, 5% will progress to chronic limb threatening ischaemia (13-15). In patients with chronic limb threatening ischaemia the one-year risk of limb amputation is 30% and five-year all-cause mortality is 50%, similar to various advanced forms of cancer (1, 2, 5-8, 12). The treatment of these high-risk individuals is shared between primary care (diagnosis, treatment of cardiovascular risk-factors, rehabilitation) and secondary care (vascular reconstruction, amputation, specialist management of cardiovascular disease).

Healthcare burden of PAD

The main causes of morbidity and mortality in PAD are limb amputations and cardiovascular events.

i) Amputations

PAD is the main cause for limb amputations (2). The lifetime amputation risk is 5% in those with both PAD and diabetes. Overall, 27,465 amputations took place in individuals with PAD between 2015 and 2018 in the UK (16). This resulted in 1.9 million bed-days between 2015 and 2018, costing the NHS £1.6 billion (16). Further to cost, any major amputation has a catastrophic effect on patients’ quality of life, and autonomy (14, 17, 18). Controlling the modifiable cardiovascular risk-factors of individuals with symptomatic PAD can reduce amputation risk by 40% (3, 5, 19, 20).

ii) Cardiovascular events

PAD shares key risk factors (smoking, hypertension, hyperlipidaemia, old age, male sex, socioeconomic deprivation and poor life-style choices) with cardiac disease and stroke (20). PAD is therefore associated with significant cardiovascular morbidity and mortality (5-7). Individuals with symptomatic PAD are those at highest risk. They are six to eight times more likely to die within ten years due to a cardiovascular event compared to age-matched patients without PAD (12, 21). The NHS treats 126,000 patients with intermittent claudication or chronic limb threatening ischaemia for a major cardiovascular event per year (Hospital Episode Statistics 2018).

These patients have regular contact with both primary and secondary care. For example, patients regularly attend GP appointments for pain relief, ulcer dressing changes, vascular outpatient clinics for scans, inpatient stays for surgery. These are all opportunities to optimise their modifiable risk-factors. The relevant NICE guidance consists of clear recommendations and targets for each risk-factor. Along the lines of the “Long Term NHS Plan” and “Making Every Contact Count” NHS initiative, we have developed an intervention specifically for PAD which aims to ensure NICE guidance is implemented at each contact with healthcare, thereby reducing future cardiovascular events, mortality, need for amputations and healthcare costs.

**How does the existing literature support this research?**

A) Literature and guidelines relating to medical treatment of PAD.

We performed two systematic literature reviews relating to PAD care (January 2019). The first review informed our research design and the second informed intervention-development. We used the NHS Evidence portal and Cochrane Library, searched the NICE library and latest available NICE, European Society of Cardiology), and American Heart Association guidelines.

Based on current NICE(3), and international guidance by several Societies (22, 23) the following treatment targets should be addressed in all individuals with symptomatic PAD – this constitutes “PAD best medical therapy”:

i) Lipid management: high-intensity statin therapy should be offered with Atorvastatin 80mg daily recommended as a first-line treatment.

ii) Antiplatelet therapy: Clopidogrel 75mg daily should be offered as a first-line therapy, unless contraindicated, in which case Aspirin 75mg or alternative antithrombotic therapy should be considered.

iii) Blood-pressure (BP) control: a BP of less than 140/90 mmHg (or 135/80 if diabetic) should be achieved, using the NICE stepwise antihypertensive medication algorithm. Salt intake should be reduced to <6g/day.

iv) Smoking cessation: All smokers should have clear information on why stopping smoking is important. Referral to a local smoking cessation programme should be offered. Varenicline should be considered alongside behavioural support.

v) Blood-glucose control: Haemoglobin A1c should be less than 48 mmol/mol (6.5%), or 53 mmol/mol (7%) for adults on a drug associated with hypoglycaemia. Pharmacotherapy should be adjusted according to the NICE algorithm. Referral to a diabetes specialist and a dietitian should also be considered.

Given the lack of up-to-date evidence from across the UK regarding the uptake of NICE guidance and the precise benefits of addressing these targets in patients with PAD, we sought to perform a national audit.

In 2017, through the Vascular and Endovascular Research Network (VERN), we audited 656 PAD patients seen in primary care across ten Clinical Commissioning Groups. Only 13% had been treated as per NICE recommendations.

We repeated the audit in 2018, attempting to assess potential benefits of treatment based on NICE guidance. Across ten regions, we found that, in 440 patients with symptomatic PAD, mean cholesterol levels were far higher above the recommended NICE levels (9). Only 12% of patients were prescribed guideline-adherent statin therapy and 39% an antithrombotic agent. We then used a prediction tool designed for patients with incident cardiovascular disease, which can predict future cardiovascular risk. The median risk of a major cardiovascular event over ten years was 53%. Had modifiable cardiovascular risk-factors been controlled as per NICE targets patients would have benefited from a 29% absolute risk reduction of their median ten year cardiovascular risk. This equates 6.3 cardiovascular disease-free years gained (9).

First-line treatment strategy of intermittent claudication

In our reviews we identified a lack of consensus regarding the optimal first-line treatment of IC. We addressed this by performing a comprehensive network meta-analysis of all published randomised studies (37 trials; 2,983 patients). We compared best medical therapy alone, percutaneous angioplasty, supervised exercise therapy, and angioplasty combined with best medical therapy. We found that best medical therapy, in the form of an antiplatelet and high-intensity statin therapy, is the most important element of care in PAD (24).

First-line treatment strategy of chronic limb threatening ischaemia

The first-line treatment of patients with chronic limb threatening ischaemia consists of urgent revascularisation, as per established international guidelines (3, 22, 23), and management of cardiovascular risk-factors over the longer term.

B) Literature to support our intervention development

Through our literature reviews we were unable to find a validated intervention developed specifically for PAD. We therefore set out to develop our own purpose-built intervention, suitable for use in the NHS, grounded on best available evidence and taking into account the needs of patients.

C) Interaction with patients and stakeholders to develop the intervention

Our background work focussed on identifying barriers and areas of good practice to develop our PAD-specific intervention. It included:

1. A patient workshop attended by 18 patients with symptomatic PAD. We discussed barriers in implementing NICE guidance, focussing on medication prescribing and adherence, blood pressure, lipid and glycaemic control. We then discussed the education that patients received following their PAD diagnosis. Finally, we discussed how barriers in implementing medical therapy could be addressed, using examples of interventions from our literature reviews. Through this process we identified the core elements of the LEGS intervention (checklist for inpatients and outpatients, structured letters to GP and a patient education leaflet), which we finalised through further PPI. A core stakeholder group of eight interested patients worked with the lead applicant to produce the patient education leaflet.

2. Between September 2018 and January 2019, a total of 191 GPs, 33 practice nurses and 12 community nurses, representing 44 clinical commissioning areas in England and Wales, filled in a structured online survey. We surveyed reasons and thresholds for patient referral to secondary care, protocols for prescribing, knowledge of NICE guidance and asked questions about barriers in adopting existing PAD guidance.

3. A structured national online survey of vascular surgeons, diabetologists, geriatricians, podiatrists, vascular ultrasound scientists, specialist vascular nurses and junior doctors in 38 tertiary referral vascular units – which represents 59% of vascular departments in the UK. We surveyed PAD prescribing protocols, specialist vascular imaging/intervention protocols, inpatient care pathways and the format of discharge summaries.

4. Face-to-face or telephone interviews of 19 GPs and 24 secondary care doctors. We mostly explored barriers in adopting NICE guidance. These doctors finalised the GP letters, inpatient and outpatient checklists, and reviewed the draft LEGS patient education leaflet.

Our work identified the following barriers:

i) Lack of communication between primary and secondary care. The GPs are often not aware that a diagnosis of PAD had been made in secondary care. There was a breakdown in communication with primary care after attending a clinic or inpatient stay. Both GPs and community nurses thought that streamlined communication through clear letters with specific action points are vital. There was near unanimous agreement that adherence to NICE guidance would be improved if it could be broken into a simple step-wise process.

ii) Patient education was poor. Patients said that either no information was given to them about PAD, their high cardiovascular risk, or the importance of medication. Some found that information given by doctors was confusing or conflicting.

iii) Prescribing in secondary care at the point of hospital discharge is inconsistent.

iv) Patients noticed medications requested by secondary care were not added onto repeat prescriptions.

v) Patients are often concerned that medication, especially statins, may have side-effects, impacting on adherence.

vi) Many doctors were not familiar with NICE PAD guidance targets.

Based on these, we used behaviour change theory, expert opinion and a taxonomy of behaviour change techniques, to match intervention strategies to each NICE treatment target. Our PPI group and research team then finalised the LEGS intervention.

# OBJECTIVES

**Research question:**

Can a purpose built intervention for patients with symptomatic PAD (the LEGS intervention) be used in routine NHS care?

**Main aim:**

The main aim of this research is to assess whether the LEGS intervention can be used in the routine care of patients who present with symptomatic PAD (i.e. intermittent claudication or chronic limb threatening ischaemia). We will therefore assess the fidelity of delivering the intervention and acceptability by patients and stakeholders.

**Secondary aim:**

This feasibility study will also produce qualitative data which will allow us to adapt the intervention to NHS care pathways and quantitative data that will inform future research assessing clinical and cost effectiveness.

**Objectives:**

5.1 The **primary objective** is to assess the fidelity of delivering the LEGS intervention in existing NHS care pathways and acceptability of each intervention component by patients and stakeholders.

5.2 The **secondary objective** is to obtain qualitative data regarding how elements of the intervention might have to be adapted for use in the NHS. Furthermore, we will produce quantitative data regarding recruitment, uptake and retention which will inform future assessments of clinical and cost-effectiveness.

5.3 **Exploratory end point**. Following completion of the research we will seek to reach formal consensus regarding how LEGS might have to be adapted and any future evaluation before wider NHS adoption. We will conduct a consensus conference where we will invite patients, experts and relevant NHS stakeholders.

# STUDY DESIGN

## 6.1 Summary of Study Design

**Patients**: Adult patients with symptomatic Peripheral Arterial Disease (PAD) referred to secondary care, either in a clinic or for inpatient treatment.

**Intervention**: We identified key barriers in both primary and secondary care, relating to the implementation of PAD guideline-based therapies. Based on this information, we developed the “LEGS” (**LE**aflet **G**p letter **S**tructured checklist) intervention, consisting of checklists, doctors’ letters and patient leaflets. LEGS aims to support patients, General Practitioners (GPs) and hospital doctors to actively manage cardiovascular risk-factors of patients with PAD. It utilises up-to-date information based on NICE guidance, easy-to-use checklists and streamlined care-pathways.

**Outcomes**:

1. Fidelity of intervention delivery (assessed quantitatively regarding adherence and qualitatively regarding overall impression/acceptability).
2. Proportion of patients agreeing to take part out of all patients invited (intervention recruitment rate)
3. Proportion of patients recruited who provide data at the end of the study period (intervention retention rate).

**Study design**: multicentre prospective cohort study including quantitative and qualitative assessments (mixed methods). Non-randomised research.

**Duration of participant participation**: Six months (i.e. until end of follow-up).

## 6.2 Primary and Secondary Endpoints/Outcome Measures

**Primary outcome measure:** Fidelity of intervention delivery (assessed quantitatively regarding adherence and qualitatively regarding overall impression/acceptability).

**Secondary outcome measures:**

Proportion of patients agreeing to take part out of all patients invited (intervention recruitment rate)

Proportion of patients recruited who provide data at the end of the study period (intervention retention rate).

Other parameters that will be recorded include (at six months): all cardiovascular events; mortality; quality of life using the EuroQol-5D (EQ-5D) questionnaire; weight and other relevant anthropometric information including Body Mass Index (BMI); blood-pressure levels; self-reported medication adherence [using the Brief Adherence Rating Scale(26)]; smoking status (self-reported with exhaled CO assessment); uptake of smoking-cessation services; anxiety (Hospital Anxiety and Depression questionnaire) and stress levels [Perceived Stress Scale(27)]; low-density and high-density lipoprotein levels as well as routine biochemistry.

# STUDY PARTICIPANTS

## 7.1 Overall Description of Study Participants

Patients recruited in this study will be adult individuals (> 18 years of age) with symptomatic PAD (i.e. intermittent claudication, ischaemic rest pain, or chronic limb threatening ischaemia), referred to secondary care, either in a clinic or for inpatient treatment.

## 7.2 Inclusion Criteria

Adult (>18 years of age) patient with incapacitating intermittent claudication or chronic limb threatening ischaemia (Rutherford stages 3–6), referred to secondary care, either in a clinic or for inpatient treatment. The participant is willing and able to give written informed consent for participation in the study. The participant has access to a telephone or computer with internet access (for those taking part in remote interviews/consensus meeting)

## 7.3 Exclusion Criteria

## The participant may not enter the study if ANY of the following apply:

Female participants who are pregnant, lactating or planning pregnancy during the course of the study.

Patients who do not have capacity to consent for themselves.

Patients with life limiting condition whereby conservative management is most appropriate.

Patients with asymptomatic PAD

# STUDY PROCEDURES

## 8.1 Informed Consent

**Patients**

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

Written and verbal versions of the participant information and informed consent will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished (at least 24 hours) to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. To allow sufficient time for potential participants to review the PIS and study information, we will contact the potential participants who are scheduled to come to a regular (elective) clinic at least one week before the appointment (telephone call). This telephone call will take place by a study collaborator who provides clinical care for PAD already and is GCP trained. It will last around ten minutes. We will inform the potential participants of this study taking place when they come to clinic and inform them that we will be placing a PIS in the post. We will give them a contact number (of the CI) if they want to ask questions in the meantime. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. For outpatients (clinics) this will take place on the date of the clinic, once the participant has confirmed they read the PIS and asked all questions they wanted to ask. For inpatients, we will give the PIS to the potential participants when they are admitted. They will have the chance to read the PIS and ask questions for at least 24 hours. We will then seek written informed consent. The person who obtained the consent will be suitably qualified and experienced, and will have been authorised to do so by the Chief/Principal Investigator as detailed on the Delegation of Authority and Signature log for the study. The original signed form will be retained at the study site within the Trial Master File (TMF) or Investigator Site File (ISF). A copy of the signed Informed Consent will be given to participants and a copy retained in the participant medical notes. A fourth copy will be sent to the patients GP to inform them of their participation in the study. We expect that COVID-19 will not have a major impact on inpatient and/or outpatient pathways for chronic limb threatening ischaemic and severe symptomatic PAD (our target population), given that these vascular pathologies are limb and/or life threatening. This has already been documented in our international study of vascular care during the COVID-19 pandemic (see: <https://vascular-research.net/projects/cover-study-covid-19-vascular-service-study/>)

**Healthcare professionals**

Healthcare professionals (doctors, nurses, healthcare assistants, physiotherapists, podiatrists, orthotists, occupational therapists, and any other qualified healthcare professions who provide some form of care for the participants of this study i.e. adult individuals with symptomatic PAD) will be recruited from the participating NHS sites to take part in qualitative interviews (qualitative part of the research). The primary investigator at each site will approach the relevant healthcare professionals during the six months of patient recruitment at each clinical NHS site (in person). A healthcare professional PIS will be handed to them and they will have at least 24 hours to think about taking part. All healthcare professional interviews will take place remotely (telephone or teleconferencing).

## 8.2 Screening and Eligibility Assessment

Participants will be identified, approached, screened and recruited by GCP trained study investigators/collaborators who will be their usual clinicians (including collaborators from the Vascular and Endovascular Research Network, research nurses, and doctors) in vascular clinics or vascular wards at each NHS site. Investigators will be listed on the Delegation of Authority and Signature Log. This study has no impact on decision making for operative or interventional therapies/treatments and follows NICE guidance treatment algorithms.

The patient’s medical notes will be screened to ensure that they have been diagnosed with symptomatic PAD (intermittent claudication or chronic limb threatening ischaemia) before they can provide written informed consent (and ensure they comply with the inclusion/exclusion criteria).

The following will be reviewed at screening and eligibility assessment stage by the study staff (research nurse and/or study collaborator):

Concomitant Medication

All prescribed medication and over-the-counter medication, vitamins, and/or herbal supplements will be recorded on CRFs when the patient has agreed to take part in the study and signed a written informed consent form. From the moment the patient has been informed about the study by the investigators/collaborators (i.e. clinicians) and has been given a PIS, they will have at least 24 hours to consider taking part. They will then be asked to either return a consent form in the post (for those who have been discharged e.g. patients seen in clinic) or provide a consent form to the investigators/collaborators in person if they are still inpatients (ward patients). Baseline information and concomitant medication will be recorded from the patients’ notes as these constitute standard information that would have been collected anyway for these patients in NHS institutions (all patients with PAD).

Physical Examination

Height, weight and temperature will be recorded.

Resting pulse and blood pressure (BP) measurements will be recorded.

This information is collected routinely for all patients with PAD who present to the NHS.

Once the patients have provided consent, these will be recorded from their notes.

Laboratory Tests

No additional laboratory tests will take place as part of this research.

Routine biochemistry results will be recorded in the CRFs including a full blood count, urea, electrolytes, estimated glomerular filtration rate, total cholesterol levels, lipid levels.

Routine biochemistry is already part of NHS care for PAD based on NICE guidance.

Radiology / Imaging Procedures

No additional procedures will take place as part of this research. Routine imaging tests and surgery/intervention(s) will be recorded in the CRFs. These images are already part of NHS care for PAD.

## 8.3 Baseline Assessments

Recruitment will last six months and will take place in the following vascular NHS regional centres and their spoke sites, providing care for patients with symptomatic PAD:

- Leicester Vascular Institute and Leicester Vascular Limb Salvage (VaLS) service,

- Guy’s & St Thomas’ NHS Foundation Trust,

- University Hospital Coventry and Warwickshire

- Dudley Hospital NHS Foundation Trust.

Patients will be recruited on vascular wards, vascular or ulcer clinics, emergency clinics, specialised CLTI clinics, and/or during on-call (e.g. by the registrar or consultant surgeon on-call).

For patients coming to a regular clinic appointment, given that they will be discharged immediately after their appointment, the study investigator/collaborator at each site will send a PIS (postal) to the patient with a CF (postal) prior to their clinic appointment (at least one week before). They will also contact the patient (telephone) to inform them of the study. On the day of the clinic, they will answer the patients’ questions, offer any clarifications, and sign a written informed consent form.

The following will be recorded in the CRFs at baseline/recruitment (once consent has been obtained) for both inpatients and outpatients:

Demographic information (age at time of recruitment, sex)

Weight/height, resting BP.

Baseline full blood count results and routine biochemistry, including total cholesterol level, and lipid profile.

Results of cross-sectional imaging relating to the arterial vasculature e.g. duplex or computed tomographic angiography(all of these are routine care).

Smoking status.

Previous operations (full surgical and vascular history).

All of the above information constitutes routine care for patients with PAD and will be recorded using their standard NHS notes.

Quality of life using the EuroQol-5D (EQ-5D) questionnaire will be documented. The study investigator/collaborator will contact the patient by phone once they have provided written informed consent in order to assess quality of life (as this is not routine care and cannot be assessed using the notes).

At this point (once the patient has been given time to read the PIS as per GCP guidance and signed a CF) the LEGS intervention documents will be given to the patients (leaflet). The doctors will also be given the relevant LEGS checklists (inpatient or outpatient checklist). The documents will be given by the investigators/collaborators named in the delegation log. They are all GCP trained healthcare professionals who already provide NHS care for PAD routinely. The LEGS checklists will be filled in by the doctors reviewing and treating the patients. A letter will be sent to the patients GP to inform them of the actions required to continue guideline management.

## 8.4 Randomisation and Codebreaking (if applicable)

This is a non-randomised study. Participants will be allocated a unique study identification number which will be site-specific, upon recruitment. This will be used in all CRFs.

## 8.5 Subsequent Assessments

**Assessment 1** – day of discharge or the day of the clinic appointment.

The number of the LEGS intervention components filled in correctly will be recorded the day the patient goes home. If this is not possible, the medical notes will be kept at the NHS site until the study team reviews the LEGS checklist to record the number of components that had not been addressed/filled in. All intervention checklists will be stored at the time of completion in the patients’ notes to ensure that they can indeed be traced and fidelity can be recorded; this includes the inpatient and outpatient forms.

30 days after discharge or after clinic appointment a 2nd copy of the GP letter will be sent to the GPs to ensure that they have received at least one copy (the same duplicate copy as the one sent on the day of discharge).

**Assessment 2** – 15 days after the day of discharge or after the clinic appointment.

The GP will be contacted (telephone) to assess whether they have received and read the LEGS intervention letter and followed the LEGS advice regarding prescribing medication. No clinical advice will be given to the GP during these telephone calls. The telephone call will be undertaken by a member of the study team. We will not ask clinicians who are not study team members to call GPs.

**Assessment 3** – Six months (follow-up).

All participants will be followed-up at six months during a routine care visit either in person (physical visit) or for those who cannot attend, remotely (telephone).

At six months, the following will be assessed on the CRFs during the patients’ appointment to see the study team:

Latest available full blood count results and routine biochemistry, including total cholesterol level, and lipid profile. No additional blood tests will be performed; these are already standard of care for patients with symptomatic PAD at six months after their initial visit.

Results of cross-sectional imaging relating to the arterial vasculature e.g. duplex or computed tomographic angiography.

Surgical and vascular history (part of standard of care).

The following will be recorded on CRFs based on information given by the patients:

Quality of life using the EuroQol-5D (EQ-5D) questionnaire.

Self-reported medication adherence [using the MARS questionnaire(26)]; smoking status (self reported); uptake of smoking-cessation services..

Recording of all concomitant medications as reported by patients.

Recording of repeat GP prescriptions.

The GP will be contacted via telephone to confirm whether they have received the study letters and information and this will be recorded at six months. This GP phone call (no clinical advice given during this phone call) will be undertaken by study staff.

**Please also refer to Appendix A and Appendix B (the LEGS intervention components).**

**Intervention fidelity assessments** (to assess primary outcome measure)

Fidelity will be assessed quantitatively by measuring staff “adherence” to each intervention component and qualitatively by assessing the “overall impression” (i.e. intervention acceptability, views, experiences) of staff/patients and staff’s ability in delivering the intervention. This is in line with recommendations regarding the optimal measures that should be used to assess fidelity of complex interventions’ delivery(1).

**Quantitative fidelity assessment**

For the quantitative adherence measurements, each component of the intervention will be assessed with regards to completion and marked accordingly. These measurements will take place at each clinic appointment (for those recruited as outpatients), on the day of discharge (for those recruited as inpatients) and at six months (final follow-up appointment). A purpose-built intervention fidelity (IF) checklist will be used to assess the delivery and the presence or absence of each intervention element. In the IF checklist, a score will be assigned to each intervention element depending on how many constituents of that element were delivered appropriately (e.g. prescription of a certain medication). We will then report proportions per patient at completion of clinical follow-up. We will also assess whether the primary care letters have been received by the patient’s practitioner at 15 days and at six months. We will cross-reference the discharge summary prescriptions to the prescriptions given to patients by primary care at their six month follow-up appointment. Finally, we will ask patients at their six month appointment to assess who had received the PAD leaflet.

**Qualitative assessments (further)**

Semi-structured interviews will be conducted to explore participants’ and providers’ experiences of receiving and delivering the intervention. This aims to evaluate the ability/feasibility of staff in delivering the intervention, overall impression, validity, usability, acceptability and engagement with the intervention. It will include barriers to engagement or delivery and ideas for improving the intervention. We will purposively sample 10 patients receiving the intervention and 10 intervention provider staff in secondary care, including junior doctors, vascular nurses and vascular surgeons (consultants). Face-to-face interviews will also be conducted with 5 GPs and primary care nurses from the three study areas with telephone interviews considered depending on the availability of the stakeholders. Patient and/or stakeholders’ interviews will not last more than two hours in each case. The recordings will be stored digitally on password controlled NHS computers at King’s College London. Transcriptions, where necessary, will be obtained using standard NHS transcription services (costed). No sensitive data will be exchanged between sites. Recruitment will cease when data saturation is reached. Topic guides will be developed, piloted and refined across the first few interviews. We will examine attitudes towards the acceptability, usability and relevance of all elements of the intervention. Qualitative data will be analysed using framework analysis. We will ask participants (using a scale) to tell us how satisfied they were with the interview on a scale of 1 to 10 (over the phone or in person depending on whether this is a remote interview or not).

COVID-19 adaptations

In case the COVID-19 pandemic places restrictions on face-to-face interviews, then we will conduct all these interviews remotely using either telephones or NHS approved software (several clinics in all the participating sites are already taking place using approved remote conferencing software). If the interviews/census meeting are undertaken face-to-face, staff, patients and healthcare professionals will be asked to wear a face-mask on arrival and wear this throughout their visit. These visits will be undertaken in a well ventilated location which allows appropriate social distancing.

## 8.6 Definition of End of Study

The end of study is the date of the last visit/ telephone follow up/ home visit of the last participant i.e. six months after the date the last patient has been recruited. Participants may be contacted for interviews, if they do provide written informed consent in that regard, for an additional three months after the end of follow-up to allow completion of the qualitative work.

## 8.7 Discontinuation/Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

Ineligibility (either arising during the study or retrospective having been overlooked at screening)

Significant protocol deviation

Significant non-compliance with treatment regimen or study requirements

An adverse event which requires discontinuation of the study or results in inability to continue to comply with study procedures

Disease progression which requires discontinuation of the study or results in inability to continue to comply with study procedures

Consent withdrawn

Lost to follow up

The reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

It is unlikely that adverse events will occur as this study follows national and international clinical guidance and standard NHS care pathways.

## 8.8 Source Data

Source documents are original documents, data, and records from which participants’ CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, computed tomographic or ultrasound scans, and correspondence with primary or secondary care. CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name. All research team members taking part in either the qualitative or quantitative parts of the study will have received Good Clinical Practice (GCP) training; the PI at each site is responsible for delivering the required training and ensuring everyone is up to date with regulatory requirements as per GCP.

# TREATMENT OF STUDY PARTICIPANTS

## 9.1 Description of Study Treatment

**The LEGS intervention**

The intervention addresses the five key treatment areas (i.e. best medical therapy) identified in our review of best available evidence and clinical guidelines, including National Institute for Health and Care Excellence (NICE) guidance:

i) Lipid control

ii) Antiplatelet therapy

iii) BP control

iv) Smoking cessation

v) Blood-glucose control.

The final LEGS intervention consists of:

i) Inpatient doctors’ checklist

One-page checklist developed with the help of Foundation Doctors, Core Surgery and Vascular Trainees, Vascular Surgery and Interventional Radiology Consultants, for patients admitted in a hospital setting. The list is filled initially with the first patient clerking (on admission) by the relevant doctor and then immediately before discharge (last day of inpatient stay).

ii) Outpatient doctors’ checklist

One-page checklist for those seen in a clinic. It has been developed with the help of two NHS Vascular Clinic Co-ordinators, a GP, Specialist Vascular Nurses, and Vascular Surgery Consultants. The list is filled in during the outpatient consultation, prompting the doctor or nurse to address all BMT key areas.

iii) LEGS leaflet for patients and relatives (both inpatients and outpatients)

A concise leaflet with information aiming to support patients to achieve their medical care targets. We used the British Heart Foundation and Circulation Foundation PAD documents as a basis, on which the patients’ helping us with the development pathway expanded as per their perceptions/preferences. The leaflet covers (in lay language) the implications of a diagnosis of PAD and the key treatment targets of NICE guidance. This is given to the patient upon the diagnosis of symptomatic PAD in the form of severe intermittent claudication or chronic limb threatening ischaemia either during their inpatient stay or at the outpatient consultation. The leaflet is also mailed to the GP and Practice Nurse. It is available in five languages.

iv) LEGS GP letter

A short standardised letter with specific action points that cover the main aspects of Best Medical Therapy for PAD. This document was developed by GPs in eleven different regions in England. The letter will be sent to the patient’s GP immediately after discharge from hospital (inpatients) or after each clinic visit (outpatient). Specific action points are suggested to the GP and Practice Nurse. The letter addresses the poor and occasionally confusing structure of secondary care communications. It will help support primary care in providing more streamlined Best Medical Therapy for those with PAD.

v) LEGS GP follow-up letter

A follow-up letter will be sent automatically to the GP four weeks after each contact with secondary care (discharge from inpatient stay or visit to the clinic), again prompting action for NICE treatment targets.

Please refer to the attached intervention elements/components (appendix A and B).

## 9.2 Storage of Study Equipment or Related apparatus

No study-specific equipment will be used or stored. Reporting will be based on standard NHS imaging policies/scans.

## 9.3 Compliance with Study Treatment

We will record patient prescriptions at six months and also record (at six months): self-reported medication adherence; smoking status; uptake of smoking-cessation services. All this information will be recorded from secondary care notes and patients (not the GP).

# SAFETY REPORTING

## 10.1 Definitions

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### 10.1.1 **Adverse Event (AE)**

An AE or adverse experience is:

Any untoward medical occurrence in a patient or clinical investigation participants, which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the the study, whether or not considered related to the study.

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### 10.1.2 **Adverse Reaction (AR)**

All untoward and unintended responses related to the study.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study qualify as adverse reactions.

### 10.1.3 **Severe Adverse Events**

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

### 10.1.4 **Serious Adverse Event or Serious Adverse Reaction**

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

* Results in death,
* Is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

* Requires inpatient hospitalisation or prolongation of existing hospitalisation,
* Results in persistent or significant disability/incapacity, or
* Is a congenital anomaly/birth defect.
* Other important medical events\*

\*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient andmay require medical or surgical intervention to prevent one of the outcomes listed above.

### 10.1.5 **Expected Serious Adverse Events/Reactions**

This study and the LEGS intervention follow established international guidance (including NHS and NICE guidance) as to what constitutes best medical therapy for PAD, and we therefore do not expect major issues with serious adverse events or reactions. Standard care NHS pathways will be followed. Minor bleeding such as bruising is expected in patients who are on therapy with an antiplatelet agent such as clopidogrel. Further, myalgia might be associated with high-dose statin therapy. These are the two most common adverse reactions which we might expect in this patient group.

### 10.1.6 **Suspected Unexpected Serious Adverse Reactions**

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information

## 10.2 Reporting Procedures for All Adverse Events

All AEs occurring during the study observed by the investigator or reported by the participant, whether or not attributed to study, will be recorded on the CRF.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to study, other suspect device and action taken. Follow-up information should be provided as necessary.

AEs considered related to the study as judged by a medically qualified investigator or the sponsor will be followed until resolution or the event is considered stable. All related AEs that result in a participant’s withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

It will be left to the investigator’s clinical judgment whether or not an AE is of sufficient severity to require the participant’s removal from treatment (see section 7.7). A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

The relationship of AEs to the study will be assessed by a medically qualified investigator.

## 10.3 Reporting Procedures for Serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs)

SAEs, with the exception of expected SAEs and SARs, must be reported to the Sponsor within one working day of discovery or notification of the event. The Sponsor will perform an initial check of the information and ensure that it is reviewed at the next R&D Management meeting. All SAE information must be recorded on an SAE form and sent to the Sponsor using the appropriate reporting form and the contact details on there. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form which must be sent to the Sponsor using the appropriate reporting form and the contact details on there.

The Sponsor will report all SUSARs to the Research Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

In addition to the expedited reporting above, the CI shall submit once a year throughout the study or on request an Annual Report to the Ethics Committee which lists all SAEs / SUSARs that have occurred during the preceding 12 months.

# STATISTICS

## 11.1 Description of Statistical Methods

After recruitment (baseline visit), participants will be followed-up at six months. Fidelity of the intervention will be reported as a proportion (with a 95% confidence interval), relating to the number of intervention elements that were delivered as intended (i.e. successfully) by the clinical team. Recruitment (proportion of patients agreeing to take part out of eligible patients screened), retention (proportion of patients who provide data at six months), uptake (proportion of patients where all parts of the intervention were completed) and participant satisfaction scores will be also be reported using descriptive statistics with 95% confidence intervals.

We will also review participants’ prescribed medication using a checklist to ensure that an antiplatelet agent and lipid-lowering medications have been prescribed as per NICE guidance algorithms. We will record patient adherence to medication using the Medication Adherence Report Scale (MARS-5); low adherence will be defined as a MARS-R score of <25. We will not ask primary care (GPs) to provide us with patient data.

Qualitative data will be transcribed verbatim and analysed (NVivo software) using framework analysis. Intervention fidelity scores will be presented as mean scores and ranges. The scores will be broken down by facilitator to examine variation between provider staff.

## 11.2 The Number of Participants

During the study recruitment period (6 months), we expect a minimum of 600 eligible patients with symptomatic PAD to be seen in a clinic or as inpatients in the three participating sites over six months, based on our prospective internal audit (May-July 2019) and the latest available National Vascular Registry (NVR) data (2018). We conservatively assume that 30% of participants will be recruited, based on the qualitative information we gathered during our extensive PPI and stakeholders’ pre-study work (interviews and focus-groups) as well as our experience from recent NIHR-funded studies with a focus on patients with symptomatic PAD in the three study sites. This will provide us with an ample size to use for qualitative interviewing. Our primary outcome of interest relates to the fidelity of intervention delivery reported at six months using the IF checklist. Fidelity will be reported as an overall proportion of the elements of the intervention that were delivered as intended. Based on our pre-study work with stakeholders and PPI, we will be willing to accept the intervention as standard of care in NHS pathways if 60% of the components are delivered as intended, whilst accepting a 10% margin of error. A total of 93 patients would have to complete the six months follow-up in order to report this within a 95% confidence interval with 90% power. Assuming a 50% retention rate, a total of 186 patients would have to be approached and consented.

## 11.3 The Level of Statistical Significance

A p value of <0.05 will be regarded as statistically significant.

## 11.4 Criteria for the Termination of the Study.

The study will stop recruitment once 186 have agreed to take part and at least 93 patients have completed six month follow-up.

## 11.5 Procedure for Accounting for Missing, Unused, and Spurious Data.

The PI will be contacted at each site in case of missing or spurious data to ensure that the information collected is precise.

## 11.6 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation from the original plan will be discussed in the regular research team meetings and reported to the Sponsor and Funder.

## 11.7 Inclusion in Analysis

All participants will be included in the final analysis as this study aims to primarily investigate fidelity of delivering a pragmatic intervention in the NHS.

# DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution, the NIHR, and the regulatory authorities to permit study-related monitoring, audits and inspections.

# QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

The University of Leicester operate a risk based audit programme to which this study will be subject.

The study research team (including the authors of this protocol and all local PIs) will meet online in two monthly intervals to ensure appropriate conduct of the study.

Data completion and quality will be reviewed once monthly by the CI together with the NIHR Leicester Biomedical Research Centre staff.

# CODES OF PRACTICE AND REGULATIONS

## 14.1 Ethics

This study is subject to NHS REC and HRA approvals before any patient can be recruited.

## 14.2 Sponsor Standard Operating Procedures

All relevant Sponsor SOPs will be followed to ensure that this study complies with all relevant legislation and guidelines

## 14.3 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

## 14.4 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

## 14.5 Approvals

Once Sponsor authorisation has been confirmed, the protocol, informed consent form, participant information sheet, GP letter and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), Health Research Authority (HRA), and host institution(s) for written approval.

Once Sponsor authorisation has been confirmed, the Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

## 14.6 Participant Confidentiality

The study staff will ensure that the participants’ anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

## 14.7 Other Ethical Considerations

Not applicable.

# DATA HANDLING AND RECORD KEEPING

All study data will be entered on a REDCap based data collection form, created specifically for the CHABLIS Study and the LEGS intervention by the NIHR Leicester Biomedical Research Centre (BRC) Bioinformatics Hub staff. As per ICH GCP (Section 5.5), all electronic data entry systems are validated and Standard Operating Procedures are maintained by the NIHR Leicester BRC.

The participants will be identified by a study specific participant number and/or code in any database. The name and any other identifying detail will NOT be included in any study data electronic file.

# STUDY GOVERNANCE

## 16.1 Study Steering Committee (SSC)

The SSC will consist of:

Mr Athanasios Saratzis (CI)

Miss Ruth Benson (Birmingham PI)

Mr Prakash Saha (London PI)

Professor Daniel Lasserson

Dr Bernadeta Bridgwood (primary care expert)

Dr Vanessa Lawrence (qualitative expert)

Patient representative (name to be confirmed)

The SSC will meet at least three monthly, either in person or remotely.

## 16.2 Data Safety Monitoring Committee (DSMC)

The DSMC will consist of:

Mr Athanasios Saratzis (CI)

Miss Ruth Benson (Birmingham PI)

Miss Susan Sterland (data expert)

The DSMC will meet at least three monthly, either in person or remotely.

# FINANCING AND INSURANCE

This study is funded by the National Institute for Health Research, the Research for Patient Benefit (RfPB) Programme.

# PUBLICATION & DISSEMINATION POLICY

This research will produce quantitative (intervention recruitment, retention, uptake) and qualitative (intervention-acceptability) data regarding the feasibility of adopting the LEGS intervention for patients with symptomatic PAD in routine NHS care. This information will be used to adapt the intervention, if necessary, for use in NHS care-pathways and guide future research relating to clinical and cost-effectiveness.

This research project is largely dependent on interaction with patients and NHS stakeholders. Both the public and a variety of NHS stakeholders have already been involved in the preliminary work, having co-developed the intervention. We will use the links that we created during the intervention development stage to ensure the public and the NHS remain engaged with the study and appropriately informed upon completion of the study.

i) Engaging patients, the wider population and the NHS

A formal lay co-applicant (patient with symptomatic PAD) has now been included in our research team. They will attend all research team meetings, support study management and ensure the conduct of the study is aligned with patients’ perceptions. They will review potential protocol amendments, lay updates and the final lay summaries of our findings.

The research team includes clinical expert co-applicants from diverse backgrounds, including primary care (Bridgwood), secondary care (Saratzis, Benson, Saha) and acute ambulatory care (Lasserson), who will lead engagement in their respective specialties. Most importantly, this research is directly linked with the Vascular and Endovascular Network (a collaborative of cardiovascular healthcare providers including nurses, doctors, allied health-professions, with presence in 44 centres across the UK) and the national GP collaborative. These two nationwide research networks will support the delivery of the research and communicate study findings regularly, ensuring engagement by all NHS stakeholders. Collaborative research groups of this nature have revolutionised the delivery of clinical research in the NHS in recent years; this formal collaboration with these two networks is a particular strength of the proposed research.

The study is also formally supported, both in terms of recruitment as well as patient engagement, by the George Davies Leicester PAD Research Group (Saratzis) and the South East London Diabetes Programme (Saha). This provides us with access to a diverse patient population of 6.5 million and established resources (research administrators, PPI co-ordinators, websites) to support wider engagement for our qualitative work, especially via the world-class resources funded by the George Davies Leicester PAD Group and the two NIHR BRCs involved in this application (Leicester and St Thomas’).

ii) Informing patients, the wider population and the NHS

Mr Saratzis in his capacity as the Vascular Society of Great Britain and Ireland (VSGBI) vice-chair of the PAD Research Specialist Interest Group will lead on disseminating to specialist NHS stakeholders. More specifically, the scientific community will receive regular updates (at least yearly) at the VSGBI, European Society of Vascular Surgery (ESVS) and Society of Vascular Nurses (SVN) meetings. A study website will be maintained, including three-monthly updates in the form of an online blog (lay and expert language) – this will link to the Vascular and Endovascular Network (VERN) website, which has an international monthly readership of >2,000 individuals, and the VSGBI website. All updates will also be linked to social media feeds managed by the NIHR Leicester BRC and VERN (>3,000 specialist and lay subscribers).

Dr Bridgwood will lead dissemination to primary care stakeholders, including the Royal College of General Practitioners (six monthly report distributed via their website and mailing lists) and national GP research collaborative (targeting GP trainees). Given the importance of engaging and informing primary care nursing networks, we will also target the Royal College of Nursing and more specifically the General Practice Nursing Forum with lay and specialist updates. Similarly, the National Association of Primary Care, providing access to both clinicians and primary care managers nationwide, will receive the same updates.

The findings of the study, once completed, will be submitted for publication in a medical journal with broad international readership across disciplines. Wherever possible, data will be published in open-access format as per NIHR policies. Anonymised open data will be shared on appropriate platforms (ClinicalStudyDataRequest and “Supporting Open-Access for Researchers” initiative). The published results will be formally communicated to the aforementioned specialist and primary care societies and networks.

How will your outputs enter our health and care system or society as a whole?

There is a clear pathway of adoption of the LEGS intervention into existing NHS care pathways, aligned with MRC and NIHR guidance. Upon completion of this research we will have gathered data regarding the feasibility of introducing a PAD-specific intervention to routine care. We will feed back the information to a group of patients and experts in the form of a consensus conference meeting. During this meeting we will report all fidelity measures and qualitative information. If the overall intervention fidelity falls below 50% we will consider extensive re-structuring before any further evaluation. If the intervention fidelity is near 60%, we will consider whether and how we will adapt the elements which had low adherence (quantitative assessment) and low satisfaction scores (interviews and questionnaires).

Future research regarding the cost-effectiveness of adopting this intervention will then be considered. The secondary outcome measures assessed in this feasibility study relating to recruitment, uptake and retention will inform a potential trial which will aim to assess clinical and cost effectiveness nationally. The design of the study will be decided and finalised during this consensus conference. The study team will then apply for funding to deliver potential future research which will guide the adoption across the NHS as standard of care. Our long-term aim is to introduce the LEGS intervention across NHS care pathways nationally in order to reduce mortality, cardiovascular events, the need for surgery (intervention) and amputations in patients with PAD. This will also have a considerable impact on quality of life and healthcare costs.

What further funding or support will be required if this research is successful?

Future research regarding the adoption of the LEGS intervention will be decided during the consensus meeting convened at the end of this feasibility study. The research team have extensive experience in hosting similar public engagement events in the NIHR Leicester BRC. Planning the exact nature of any future evaluation without the information gathered during this feasibility study is unrealistic, given the complexities relating to PAD care, both in terms of patients’ characteristics and the pathways of healthcare delivery. Even though the intervention constituents are based on NICE guidance, best available evidence, patients’ and staff experiences, the intervention as a whole has not been assessed in the NHS before.

In the consensus meeting, we will invite patients, experts (including methodologists) and stakeholders involved in PAD care pathways (community, primary and secondary care). We will also invite representatives from the Royal Colleges of General Practitioners and Surgeons, VSGBI, NICE, and NHS England. Research findings will be presented and consensus will be sought regarding the need as well as design of future evaluation relating to clinical and cost effectiveness. Should the fidelity of intervention delivery exceed 50% with limited adjustments to the elements, we will proceed directly with an effectiveness evaluation via the NIHR Health Services and Delivery Research or the Health Technology Assessment Programme. In case the fidelity is below 50% with considerable concerns raised in the qualitative assessments, the consensus meeting will guide the restructuring of the intervention and future evaluation accordingly.

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# APPENDIX A: STUDY FLOWCHART

# APPENDIX B: SCHEDULE OF PROCEDURES

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Procedures | **Visits** | | | | |
| **Screening** | **Baseline** | **Day of clinic** | **Discharge date** | **6 months** |
| Informed consent | **x** | **x** |  |  |  |
| Demographics | **x** | **x** | **x** | **x** | **x** |
| Medical history | **x** | **x** | **x** | **x** | **x** |
| Quality of Life questionnaire |  | **x** |  |  | **x** |
| Medication questionnaire |  |  |  |  | **x** |
| Concomitant medications | **x** | **x** | **x** | **x** | **x** |
| Physical examination |  | **x** | **x** | **x** | **x** |
| Laboratory tests |  | **x** |  |  |  |
| Eligibility assessment | **x** |  |  |  |  |
| Compliance |  |  |  |  |  |
| Adverse event assessments |  |  | **x** | **x** | **x** |