Ankle Arterial Doppler Waveform Assessment For Surveillance Following Lower Limb Revascularisation: WAVE study

Ankle Doppler waveform test for lower limb PAD revascularisation surveillance

STUDY PROTOCOL

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STUDY COORDINATION CENTRE: Department of Surgery and Cancer, Imperial College London, London
Imperial Vascular Unit, Imperial College Healthcare NHS Trust, London
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Protocol authorised by:

Name & Role	Date	Signature
Principal investigator: Pasha Normahani	01/03/2024	

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Clinical Queries

Clinical queries should be directed to Hamidah Alodayni, who will direct the query to the appropriate person

Revision summary

Protocol version	Date	Revision summary
V.1	15/11/2023	N/A – Original protocol
V.2	18/12/2023	-Primary outcome measure clarifications -Further details on statistical analyses - Addition of co-investigators -Additional secondary objectives -Create the study flowchart
V.3	07/02/2023	-Include sample size calculations -Addition of study statistician Mr Nicholas Johnson -Expanded on procedures and Assessments -Clarification of study visits
V.4	01/03/2024	-Additional secondary objectives -Updated background section with additional literature -Updated study flowchart

Sponsor

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

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This protocol describes the Ankle Arterial Doppler Waveform Assessment For Surveillance Following the Lower Limb Revascularisation study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

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

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STUDY SUMMARY

TITLE Ankle Arterial Spectral Waveform Assessment For Surveillance Following Lower Limb Revascularisation

DESIGN Single centre, prospective, observational, diagnostic accuracy study

AIM To evaluate the feasibility and accuracy of using ankle arterial spectral waveform assessment for surveillance following lower limb revascularisation

OBJECTIVES

Primary objective

The primary objective of this study is to determine the diagnostic performance of serial ankle visual arterial Doppler waveform assessment (using a handheld continuous-wave Doppler device) for the detection of significant arterial restenosis, as a method of post revascularisation surveillance, as determined by a full arterial lower limb Duplex Ultrasound (DUS).

Secondary objectives

- To determine the cost-effectiveness of serial visual handheld Doppler ankle waveform assessment over an appropriate time horizon of five years
- To determine the diagnostic performance of serial visual focused ankle duplex ultrasound waveform assessment (visual waveform assessment using pulsed-wave Doppler)
- To determine the cost-effectiveness of point of care duplex ultrasound waveform assessment over an appropriate time horizon of five years
- To determine the diagnostic performance of serial visual waveform assessment using exploratory diagnostic thresholds
- To evaluate the patient's acceptability of the test
- To evaluate the effect of confounding patient characteristics (e.g., neuropathy and ulceration) on diagnostic performance
- To evaluate the performance of the test for establishing the severity of stenosis
- To evaluate inter- and intra-rater reliability of index tests and evaluate inter- rater reliability of reference test
- To determine the prognostic value of serial visual waveform assessment in predicting lower limb events (e.g. secondary revascularisation, wound healing, major lower limb amputation)
- To evaluate the use of serial visual waveform assessment as a surrogate measure of technical revascaulrisation success
- To evaluate the application of machine learning and signal processing methods to classify arterial waveforms

OUTCOME MEASURES

Primary outcome measure

The primary outcome is the sensitivity of index tests as compared to the reference test of a full lower limb arterial

DUS.

Secondary outcome measures

- Specificity, likelihood ratios, predictive values and diagnostic odds ratio.
- Health economic outcomes: Cost of the test, quality-adjusted life and Incremental Cost-Effectiveness Ratio (ICER) at five years
- Patient acceptability of index tests (Likert scale)
- Inter- and intra-rater reliability of index tests and inter-rater reliability of reference test
- To establish optimal visual waveform criteria for the diagnosis of restenosis

ELIGIBILITY

Inclusion

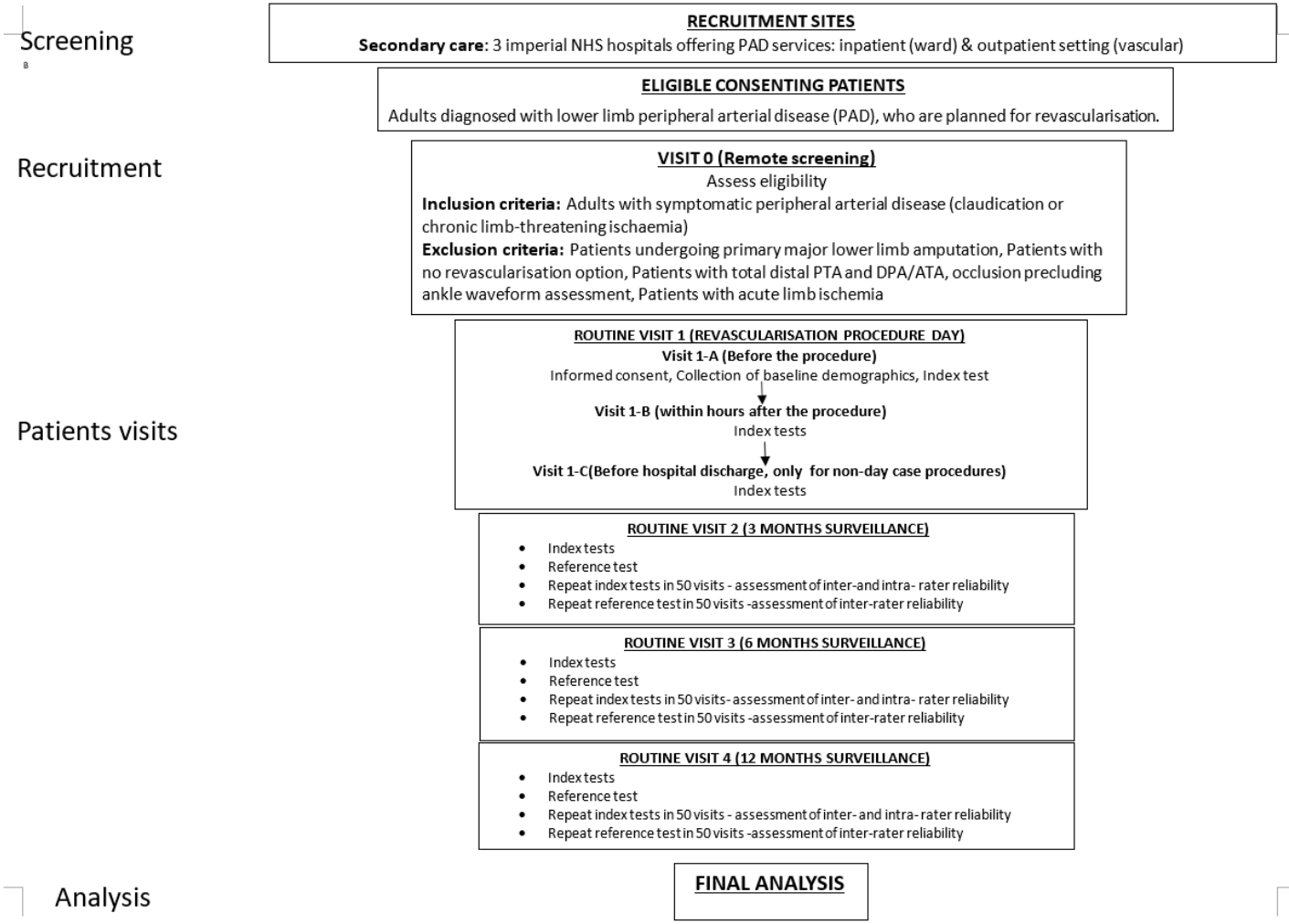
- ≥18 years or older (no upper age limit)
- Diagnosis of peripheral arterial disease based on duplex ultrasound, CTA, MRA or intra-arterial digital subtraction angiography
- Patients presenting with symptomatic peripheral arterial disease (short distance claudication or chronic limb-threatening ischaemia) who are planned to undergo primary lower limb arterial revascularisation
- Patients presenting to vascular services (inpatient or outpatient settings)

Exclusion

- Patients undergoing primary major lower limb amputation
- Patients with no revascaulrisation option
- Patients with total distal ankle vessel (posterior tibial artery,PTA; anterior tibial artery, ATA; peroneal artery, PA) occlusion precluding ankle waveform assessment
- Patients with acute lower limb ischemia
-

DURATION 24 months: 12 months recruitment and 12 months follow up.

Reference diagram



1. INTRODUCTION

1.1. Background

Peripheral Artery Disease (PAD) represents a prevalent global health issue, particularly among the ageing population. Roughly one in five individuals aged 60 and above in the UK is estimated to be affected by PAD, with this demographic facing a 2 to 4 times higher risk of myocardial infarction, stroke, and coronary artery disease(1).

Peripheral Artery Disease (PAD) in the lower extremities is a prevalent manifestation of systemic atherosclerosis. It could manifest as claudication, rest pain, and/or gangrene(2). PAD can significantly impact an individual's quality of life, particularly due to symptoms like limb claudication. This can limit mobility and daily activities. Detecting Peripheral Artery Disease (PAD) at an early stage facilitates the initiation of treatment and the adjustment of risk factors, thereby reducing the cardiovascular disease risks associated with the condition(3). In addition, it empowers healthcare providers to monitor PAD progression and conduct regular follow-up appointments for continuous management and preventive actions(4).

Treatment for Peripheral Artery Disease (PAD) involves a comprehensive approach to address symptoms and minimise cardiovascular risks. Crucial interventions such as revascularisation procedures, encompassing angioplasty and bypass surgery, have become pivotal in reinstating blood flow and alleviating symptoms among individuals suffering from lower limb PAD(3). Individualised treatment plans necessitate collaboration with healthcare professionals to ensure comprehensive and personalised care.

Surveillance post-revascularization refers to the ongoing monitoring and assessment of individuals who have undergone a revascularisation procedure to treat Peripheral Artery Disease (PAD) or other vascular conditions. The main objective of follow-up is to identify clinically important issues before clinical signs and symptoms become apparent, at an early stage when they can be managed most safely and effectively. This is essential for evaluating the effectiveness of the intervention, detecting potential complications such as restenosis, and ensuring long-term vascular health(5).

Routine clinical assessments, encompassing physical examinations and ankle-brachial index measurements, are commonly utilised to assess disease progression. Non-invasive imaging modalities like Doppler ultrasound or magnetic resonance angiography are mostly employed to visualise blood flow and identify any arterial blockages or irregularities(4). Additionally, despite these different surveillance strategies, rates of lower limb amputation , morbidity , mortality following lower limb revascularisation remain similar(6,7). The frequency and duration of post-revascularization surveillance depend on various factors, including the type of intervention, the severity of the disease, and the individual patient's risk profile(8). The optimal follow-up strategy for individual patients should strive to reduce, potential risks, associated costs, and any interference with the patient's daily life. However, the

optimal form and frequency of structured follow-up programmes have remained controversial, mostly due to a lack of definitive evidence(9).

1.2. Rationale for current study

Non-invasive approaches are the most favoured diagnostic and monitoring methods for Peripheral Artery Disease (PAD)(5). Individuals presenting with a medical history and physical examination consistent with PAD undergo initial assessment using arterial Duplex ultrasonography (DUS). DUS is advantageous as it doesn't involve contrast or radiation exposure and generates portable and reproducible images. DUS offers two-dimensional structural images to assess for visual arterial stenosis and haemodynamic information from Doppler signals(9). These signals are analysed through spectrum analysis and colour flow velocity mapping. Spectrum analysis involves quantitative and qualitative interpretation of the visual arterial spectral waveform. It precisely identifies the location and severity of arterial stenosis along the lower limb, distinguishing between different grades of stenosis and occlusion(5). DUS offers essential anatomic and hemodynamic information vital for strategic revascularisation planning. Moreover, DUS serves as a valuable tool for post-procedural surveillance, including cases involving angioplasty, stent placement, and bypass grafting.

Full lower limb DUS for surveillance following lower limb revascularisation is technically challenging and must be carried out in specialised vascular departments(10). It is therefore costly to perform and unwell-liked by patients, resulting in high dropout rates(11). Previous studies have demonstrated that a focused assessment of the visual arterial waveform at the ankle is highly accurate and cost-effective for the diagnosis of PAD(12). Changes in the quality of blood flow at the ankle reflect upstream steno-occlusive arterial disease. However, this technique has not been yet evaluated for the purpose of surveillance following lower limb revascularisation. If serial assessment of visual ankle arterial waveforms was accurate, it could potentially allow for cheaper, more regular surveillance outside of the hospital setting.

The primary aim of this study is to determine the diagnostic performance of serial visual handheld Doppler ankle waveform assessment for the detection of significant arterial stenoses as a method of post-revascularisation surveillance, as determined by a full arterial lower limb Duplex Ultrasound.

2. STUDY OBJECTIVES

2.1. Primary objective

The primary objective of this study is to determine the diagnostic performance of serial ankle visual arterial Doppler waveform assessment (using a handheld continuous-wave Doppler and pulsed-wave Doppler device) for the detection of significant arterial restenosis as a method of post-revascularisation surveillance, as determined by a full arterial lower limb Duplex Ultrasound (DUS).

2.2. Secondary objectives

- To determine the cost-effectiveness of serial visual handheld Doppler ankle waveform assessment over an appropriate time horizon of five years.
- To determine the diagnostic performance of serial visual focused ankle duplex ultrasound waveform assessment (visual waveform assessment using pulsed-wave Doppler).
- To determine the cost-effectiveness of point-of-care duplex ultrasound waveform assessment over an appropriate time horizon of five years.
- To determine the diagnostic performance of serial visual waveform assessment using exploratory diagnostic thresholds.
- To evaluate the patient's acceptability of the test.
- To evaluate the effect of confounding patient characteristics (e.g., neuropathy and ulceration) on diagnostic performance.
- To evaluate the performance of the test for establishing the severity of stenosis.
- To evaluate inter- and intra-rater reliability of index test tests.
- To evaluate inter-rater reliability of reference test
- To determine the prognostic value of serial visual waveform assessment in predicting lower limb events (e.g. secondary revascularisation, wound healing, major lower limb amputation).
- To evaluate the use of serial visual waveform assessment as a surrogate measure of technical revascularisation success.
- To evaluate the application of machine learning and signal processing methods to classify arterial waveforms.

3. STUDY DESIGN AND SETTING

- Prospective observational study of hospitalised and non-hospitalised patients with peripheral arterial disease post-revascularisation.
- The study aims to recruit 121 individuals.
- The study will run for 24 months.
- This study is open to all patients (Outpatient and Inpatient settings) at NHS Trust, meeting specific inclusion and exclusion criteria.

4. STUDY OUTCOME MEASURES

4.1. Primary outcome

The primary outcome is the sensitivity of index tests compared to the reference test of a full lower limb arterial DUS.

4.2. Secondary outcomes

- Specificity, likelihood ratios, predictive values and diagnostic odds ratio.
- Health economic outcomes: Cost of the test, quality-adjusted life and Incremental Cost-Effectiveness Ratio (ICER) at five years
- Patient acceptability of index tests (Likert scale)
- Inter- and intra-rater reliability of index tests
- inter-rater reliability of the reference test
- To establish optimal visual waveform criteria for the diagnosis of restenosis

5. PARTICIPANT ENTRY

5.1. Inclusion criteria

- ≥18 years or older (no upper age limit)
- Diagnosis of peripheral arterial disease based on duplex ultrasound, CTA, MRA or intra-arterial digital subtraction angiography.
- Patients presenting with symptomatic peripheral arterial disease (short distance claudication or chronic limb-threatening ischaemia) who are planned to undergo primary lower limb arterial revascularisation.
- Patients presenting to vascular services (inpatient or outpatient settings).

5.2. Exclusion criteria

- Patients undergoing primary major lower limb amputation.
- Patients with no revascaulrisation option.
- Patients with total distal ankle vessel (posterior tibial artery, PTA; anterior tibial artery, ATA; peroneal artery, PA) occlusion precluding ankle waveform assessment.
- Patients with acute lower limb ischemia.

5.3. Withdrawal criteria

Upon enrolment, the clinical trial site will make diligent efforts to maintain communication with participants throughout the 24-month study duration. Participants will be provided with a study helpline to address any concerns. However, an anticipated 15% of participants may be lost to follow-up. Participants retain the freedom to withdraw from any aspect of the study without impacting their regular medical care.

TheChief Investigator (CI) has the authority to withdraw participants from the study to safeguard their safety or if participants are unwilling to adhere to the protocol. In the event of withdrawal or discontinuation, all participants will be considered off the study tests but on study and will continue to be monitored until the study concludes (24 months), unless they explicitly withdraw consent for further follow-up. Any changes in their status and the study procedures or assessments from which they have withdrawn will be documented in the Case Report Form (CRF)/electronic CRF and, if provided by the participant, in their medical records.

6. ADVERSE EVENTS

6.1. Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject 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 hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

6.2. Reporting procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs
All such events, whether expected or not, should be recorded

5.3.2 Serious AEs
An SAE form should be completed and emailed to the principal Investigator within 24 hours. However, relapse and death and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the < name of REC>where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
RGIT@imperial.ac.uk
Please send SAE forms to: Pasha Normahani
Tel: 07983402262 (Mon to Fri 09.00 – 17.00)
E-mail: p.normahani@imperial.ac.uk

7. INTERVENTION AND FOLLOW-UP

7.1. Index test technique

Visual ankle arterial waveform assessment will be performed by the researcher (who is a trained vascular scientist) or clinical vascular scientist assessing the patient as part of their routine clinical assessment. Visual ankle arterial waveform assessment (index test) will be conducted using two different methods: with a handheld continuous-wave Doppler device (CWD) and using Duplex ultrasound pulsed-wave Doppler (PWD) (Figure 1).

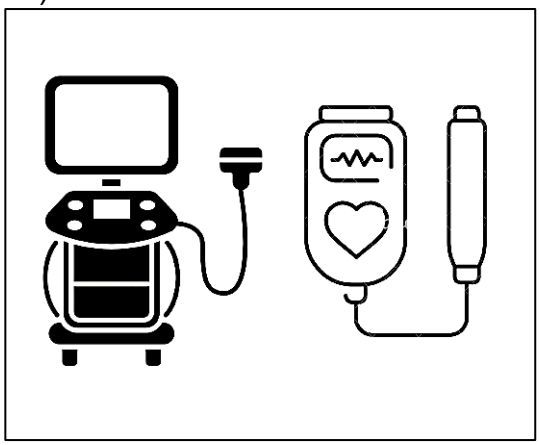


Figure 1.Illustration for the ankle doppler waveforms test devices. Left: Ultrasound Machine probe (PWD). Right : the handheld doppler device (CWD).

The test will be performed in one or both lower limbs, depending on whether the patient has undergone unilateral or bilateral revascularisation. The anterior tibial, posterior tibial, and peroneal arteries will be interrogated at the ankle using a standard technique. Before the procedure, the patient is typically positioned in a supine position with the ankle to be examined exposed and rested for at least 10 minutes prior to the test. The examination will be conducted in a standard room temperature between 20°C to 22°C to avoid the influence of temperature on peripheral vessels.

The procedure involves applying ultrasound gel to the ankle, followed by the placement of a Doppler ultrasound (PWD) or handheld (CWD) probe over specific locations on the ankle to assess blood flow in the arteries. For the handheld Doppler, the probe will be placed at a 45° angle to the ankle vessels, and the vascular scientist may make adjustments to the position of the probe to optimise the clarity of the continuous Doppler signals. Then, the visual and audio signals will be generated and optimised by the device algorithms.

When using Doppler ultrasound, arterial spectral waveforms will be sampled from each vessel's centre using a Doppler angle of <60°. Waveforms will be optimised for interpretation by adjusting sample volume, sample size, Doppler scale, Doppler gain, and wall thump filter settings. The entire scanning process usually takes approximately 10 to 15 minutes for both tests.
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7.2. Index test diagnostic criteria and analysis

By comparing Doppler waveforms recorded at different time intervals, changes that indicate restenosis can be detected , such as changes in waveform morphology or velocity. The patterns and properties of the Doppler waves produced during the tests will be analysed. Doppler waveforms will be analysed according to their auditory and/or visual characteristics, which undergo alterations in the presence of stenosis. In analyses of audio signals, non-pathological Doppler waveforms will be regarded as multi-phasic, encompassing both bi-phasic (two) and tri-phasic (three) sounds Conversely, a monophasic waveform, representing a single sound, will be considered pathological, indicating the potential presence stenosis. During the visual analysis of Doppler waveforms, non-pathological waveforms will continue to exhibit a distinct shape indicative of high resistance and diastolic flow reversal, falling into the category of multiphasic (bi or tri-phasic). Conversely, pathological waveforms are expected to display low resistance, slow systolic acceleration, and the absence of diastolic flow reversal, classifying them as monophasic.

7.3. Data collection

Visual waveform signals will be collected and saved on a Micro SD card from the handheld Doppler device. For visual waveforms obtained by the Duplex ultrasound machine, screenshot images of the visual waveform output will be collected and saved, or the data will be saved directly to external media, such as USB drives or SD memory cards. Then, data will be collected on portable storage devices and promptly will be transferred to more secure storage systems after each session.To allow for the collection of the Doppler audio signal, which will be used in later phases of this research, the handheld Doppler device will be connected to a computer device using a rig set-up that converts the stereo output to digital audio

7.4. Incidental findings

Incidental findings may potentially be identified during study assessments for example, lesions detected on ultrasound exam. These will be reported to the local clinical team and the GP.

7.5. Repeating index test

To assess both inter- and intra-observer reliability, the index test will be repeated on the same day by the same operator as well as by different operators. This will be performed across 50 episodes or visits involving volunteer patients during the three follow-up visits (visits 2, 3, and 4). We anticipate that this additional procedure will extend the duration of each episode by approximately 30 minutes.

7.6. Reference test

Patients will undergo a full departmental arterial DUS at their respective hospitals on the same day as the index tests by one vascular scientist. The study will assess the inter-observer reliability of the reference test by having it repeated by different vascular scientists. This reference scan is part of the standard care they will receive as part of follow up program following lower limb revascaularisation present in each clinic. All lower limb arterial segments (Iliac, femoral, popliteal and tibial) will be assessed using a combination of B-mode, Colour Doppler and Spectral Doppler ultrasound in transverse and longitudinal planes. Peak Systolic Velocity (PSV) will be selectively sampled throughout the segments and at areas of suspected stenosis. Peak systolic velocity ratio (PSVR) will be calculated as the ratio of PSV at the site of stenosis to where the lowest pre- or post-stenotic PSV value will be measured. All reference scans will be performed using departmental duplex ultrasound machines.

7.7. Repeating reference test

In addition to the index test, the reference test will be repeated on the same day by a different operator to assess inter-rater reliability. This will be performed during the three follow-up visits (visits 2, 3, and 4) in 50 episodes or visits with some

volunteering patients. We anticipate that this will extend the usual procedure by approximately 30 minutes.

8. STATISTICS AND DATA ANALYSIS

8.1. Sample size

The calculations considered a 95% confidence level (equivalent to a 5% margin of error), an assumed restenosis rate of 44.05%, and an anticipated sensitivity of 90% for the visual Doppler waveform assessment (index test) based on our prior investigations. The determined sample size was calculated to be 314. Accounting for an expected attrition rate of 15% derived from previous research(12), the target recruitment for this study is set at 362 episodes or visits.
However, as we treat the three surveillance periods as independent episodes (patients with diagnosed restenosis will go on to have treatment), and given that each recruited patient will have three episodes or visits of surveillance during the follow-up, the actual number of participants who will need to be recruited is 121 patients.

8.2. Statistical plan and data analysis

Any missing data will be appropriately justified, documented, and excluded from the analysis. The results of the index test will be cross-tabulated with those of the reference test. Uncertainty will be measured by calculating 95% confidence intervals using R package ‘epiR’. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) will be computed for different cut-off values of the index test.

Comparison of diagnostic performance between the index tests and the reference test will be conducted using the 'DTComPair' R package. Sensitivity will be compared between the index test and the reference test through the application of McNemar and exact Binomial tests. Likelihood ratios will be compared between the index test and the reference test using a regression model approach.

The Cohen’s Kappa test will be employed to evaluate the agreement between the two approaches of index test and the reference test. The interpretation of Kappa values will be as follows: K values in the range of 0.21-0.40 will indicate fair agreement, K values in the range of 0.41-0.60 will signify moderate agreement, K values in the range of 0.61-0.80 will represent substantial agreement, and K values in the range of 0.81-1.00 will suggest almost perfect agreement.

The potential impact of confounding patient characteristics (such as age, gender, intervention procedure and minor amputation history) on the performance of the index test will be evaluated using a logistic regression approach. This method involves a

modified formulation of logistic regression that facilitates the computation of likelihood ratios for the index test, considering selected covariates. The technique entails estimating logistic regression models for both the prior and posterior odds of disease. The model for prior odds is based on patient characteristics, while the model for posterior odds incorporates the diagnostic test under consideration.
Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8.3. Cost-effectiveness analysis

A discrete-time state-transition (Markov) model will be employed in the study to compare the health service costs and quality-adjusted life years (QALY) associated with different index tests methods. The objective is to determine which method offered the greatest mean net benefit. The construction of the model will be involved extensive discussions among an interdisciplinary team of health economists and clinicians. The decision model have a time horizon of 5 years, with costs and QALYs discounted at a rate of 3.5% per year. The reference price-year is 2022/23, and the perspective adopted is that of the United Kingdom (UK) National Institute for Health and Care Excellence (NICE) and Personal and Social Services. The study adheres to the reporting standards outlined in the Consolidated Health Economic Evaluation Reporting Standards.

8.4. Machine learning

Following the completion of the primary study, we will evaluate whether arterial waveform signals can be automatically classified using the application of signal processing and machine learning methodologies. Index test signals will be labelled using the results of the reference test and different machine learning methodologies deployed and compared for accuracy of classification.

9. RECRUITMENT AND PARTICIPANT TIMELINE

Recruitment will be primarily from vascular outpatient clinics as well as inpatient wards. We estimate that the study will be completed within 24 months of commencement where one year for recruitment and one year follow up. To recruit 121 patients evenly across 12 months, aiming for approximately 10 patients per month. The end of the study is defined as the last recruited patient completing the follow-up at 12 months.

9.1. Visit 0 (Pre-screening)

Adults with PAD will be pre-screened at least 74 hours prior to their routine (visit 1A) by a member of the direct care team. If eligible for recruitment and willing to speak to a research nurse. If the patient is willing, the study will be explained. If the patient gives verbal consent to receiving study information material, these will be provided on visit 1A, which coincides with a routine/planned visit. They will be told that if they agree to partake in the study and that if they choose not to participate, this will not affect their usual clinical care.

9.2. Routine visit 1(Planned clinical admission for revascularisation)

Patients undergoing lower limb revascularisation may be admitted for a day-case procedure (most endovascular procedures) or longer inpatient admission (all open surgical procedures). All patients will have study assessments prior to (visit 1A) and shortly after their procedure (visit 1B). This is to assess for immediate changes in the arterial waveform following revascularisation. Additionally, for those who are planned day cases, a baseline waveform will be established for later study visits so that serial waveform comparisons can be made. Patients who are planned for a longer admission will also have a later assessment (visit 1C) prior to discharge. This is because they may undergo further revascularisation procedures, resulting in further changes to the arterial waveform.

Visit 1-A

On visit 1A, informed consent will be obtained before the participant undergoes revascularisation procedures. Following this, demographic data will be collected, and then clinical assessment such as medical, intervention and drug history will be obtained as well as in the next routine visits. Then, patients will undergo the index tests (visual waveform assessment using continuous-wave handheld Doppler and pulsed-waved Doppler focused DUS). The visit schedule is summarised in a table (Appendix 1).

Visit 1-B

Following the revascularisation, patients will be expected to have their index test in both approaches after several hours.

Visit 1-C

Prior to hospital discharge, patients will undergo the index test in both approaches. This criterion is applicable exclusively to patients undergoing non-day case procedures, who will be discharged subsequent to a period of several days.

9.3. Routine visit 2,3,4 (3,6,12 months surveillance, respectively)

Patients will be followed up at 3, 6 and 12 months as per standard national and local policies. At these visits, they will undergo routine surveillance with a full lower limb DUS performed by a clinical vascular scientist, as per current practice. In addition, they will undergo the index tests on the same day. We expect that this will add an additional 15 minutes to the usual episode. In 50 episodes or visits , some volunteering patients will undergo repeated index tests and reference test to assess the tests reliability.

9.4. Blinding

The researcher or the vascular scientists who performing the index tests will be blinded to the results of the reference test. Additionally, the vascular scientist performing the reference test will be blinded to the results of the index test. In addition, the independent findings of the researcher, vascular scientist and clinician including history, examination and referenced Duplex ultrasound test will be kept blinded from one another.

10. REGULATORY ISSUES

10.1. Ethics approval

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

10.2. Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw from the protocol treatment at any time without giving reasons or prejudicing further treatment.

10.3. Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. Data will be pseudonymised Data will not be transferred to a third party.

10.4. Indemnity

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

10.5. Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.Travel expenses for study visits will be reimbursed as required.Individual researchers do not receive any personal payment beyond their normal salary or other benefits for participating in this research. This policy helps maintain the integrity of the research

by avoiding potential conflicts of interest that could arise from financial incentives for researchers.

10.6. Funding

Hamidah Alodayni is funded by the Government of Saudi Arabia (Royal Embassy of Saudi Arabia in London). Pasha Normahani is funded by an NIHR Clinical Lectureship. Infrastructure support for this research was provided by the NIHR Imperial Biomedical Research Centre (BRC). The funders play no role in shaping the study's design and are not involved in any aspect of data collection, data analysis, or the formulation of the study protocol and manuscript.

10.7. Audits

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

11. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Hamidah Alodayni.

12. PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the CI. Terms of authorship will be agreed with all contributors. Authorship of parallel studies initiated will be according to the individuals involved in the project but must acknowledge the contribution of the study. The study will be published in a peer reviewed journal, and available from the researchers on request. We also intend to create an internal report for IC, summarizing the methodology, results, and implications of the study for internal use and reference. A lay summary of the results will be provided to participants.

13. REFERENCES

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14. APPENDICES

Appendix 1. Participants visits schedule

PROCEDURES AND ASSESSMENTS	VISIT 0 PRESCREENING / IDENTIFICATION	ROUTINE VISIT 1 REVASCULISATION DAY			ROUTINE VISIT 2 3 MONTHS SURVEILLANCE	ROUTINE VISIT 3 6 MONTHS SURVEILLANCE	ROUTINE VISIT 4 12 MONTHS SURVEILLANCE
		Visit 1-A (Before the procedure)	Visit 1-B (within hours after procedure)	Visit 1-C (Before hospital discharge, only for non-day case procedures)			
Pre-screening	X						
Inclusion & exclusion criteria	X						
Informed Consent		X					
Demographics		X					
Index test with handheld doppler		X	X	X	X	X	X
Index test with Ultrasound machine		X	X	X	X	X	X
Repeat of index tests (same operator)					X	X	X
Repeat of index tests (different operator) *					X	X	X
Reference test DUS					X	X	X
Repeat of reference test DUS (same operator)*					X	X	X

*Only relevant in the first consenting 50 (out of 362 total) visits.