CLINICAL STUDY PROTOCOL

Full Study Title: Diagnostic tools to establish the presence and severity of peripheral arterial disease in people with diabetes

Short Study title / Acronym: DM PAD

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This protocol describes the DM PAD trial and provides information about procedures for enrolling participants to the trial. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres enrolling participants for the first time are advised to contact the Trial Coordination centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the Trial Coordination centre.

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
DMEC	Data Monitoring and Ethical Committee
ECTU	Edinburgh Clinical Trials Unit
eCRF	Electronic Case Report Form
EQ-5D-5L	European Quality of Life-5 dimensions 5 Level
HRA	Health Research Authority
ICHNT	Imperial College Healthcare NHS Trust
ICMJE	International Committee of Medical Journal Editors
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SAG	Special Advisory Group
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
TrEAD	TEsting for Arterial disease in Diabetes study
PAD-scan	Podiatry ankle duplex scan
ABPI	Ankle-brachial pressure index
TBPI	Toe-brachial pressure index
TcPO2	Transcutaneous pressure of oxygen
PPI	Patient and publica involvement
MRA	Magnetic resonance angiograph
CTA	Computed tomography angiography
eGFR	Estimated glomerular filtration rate
QALY	Quality Adjusted Life Years
WIfI	Wound, ischaemia, and foot infection

NHS	National Health Service
RGIT	Research Governance and Integrity Team

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TRIAL SUMMARY

TITLE
Diagnostic tools to establish the presence and severity of peripheral arterial disease in people with diabetes

OBJECTIVES

Primary:

To determine the diagnostic performance of index tests (audible handheld Doppler, visual handheld Doppler, ABPI, exercise ABPI and TBPI) for the diagnosis of PAD in patients with diabetes as determined by a reference test (CTA or MRA).

Secondary:
- To determine the cost-effectiveness of tests
- To determine the performance of tests using exploratory diagnostic thresholds
- To explore the effect of combining different tests on diagnostic performance
- To evaluate patient acceptability of tests
- To evaluate the effect of confounding patient characteristics (e.g., neuropathy and ulceration) on diagnostic performance
- To evaluate the performance of tests for establishing the severity of PAD
- To evaluate inter- and intra-rater reliability of tests
- To evaluate the performance of PAD-scan (in selected centres).

DESIGN

Prospective multicentre diagnostic accuracy study

SAMPLE SIZE
A total of 730 participants

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria:
- Aged ≥18 years
- Known history of diabetes

Exclusion criteria:
- PAD status known on imaging
- Known history of PAD intervention
- CTA and MRA contraindications- renal impairment, pregnancy, contrast medium hypersensitivity/allergy, non-compatible implants (MRA only).
- Unable to provide appropriate informed consent.
- Interim surgical interventions (occurring in the time interval between index and reference tests) will be considered a protocol violation and patients will be excluded.

MAIN STUDY PROCEDURES (including intervention duration and follow-up)

VISIT 0

- Remote screening

VISIT 1 (will occur at a routine/planned visit):

- Eligibility check
- Recording of demographic detail and medical history
- Assessment for neuropathy
- Assessment of diabetic foot ulcer severity, if relevant
- Quality of Life questionnaire: the validated EuroQoL (EQ-5D-5L) questionnaire will be used to assess the generic QoL and will allow economic assessment
- Index tests for the diagnosis of peripheral arterial disease:
    1. Audible handheld Doppler
    2a. Visual handheld Doppler
    2b. PAD-scan (only in 4 selected centres)
    3. ABPI
    4. TBPI
    5. Exercise ABPI i.e., ABPI performed following repetitive heal raising.
- Patient acceptability; patients will be asked to rate their experience of each test on a Likert scale
- Blood test to assess renal function*
- Repeating of index tests by the same and by an alternative operator for the assessment intra- and inter-rater reliability, respectively (only performed in the first 100 volunteering patients)

*In some centres, the blood test to assess renal function may require a separate visit.

VISIT 2 (Within 6 weeks of visit 1)

- Reference scan (MRI or CTA)

OUTCOME MEASURES

Primary outcome

- Sensitivity of index tests

Secondary outcome(s)

- Specificity, likelihood ratios, predictive values and diagnostic odds ratio
- Health economic outcomes: 1) Cost of the test, including direct costs and amortisation of capital equipment and use of other healthcare resources for prevention and treatment of the disease over a time horizon of 5 years 2) Quality Adjusted Life Years at 5 years. 3) Incremental cost-effectiveness ratio at 5 years
- Patient acceptability
- Technical success
- Inter- and intra-rater reliability

1. BACKGROUND

Diabetes is a major global healthcare issue with an estimated prevalence of 9.3% (1). Over 6% of people with diabetes develop a diabetic foot ulcer (DFU) (2). DFUs are slow to heal (3), have a negative impact upon patients quality-of-life (4) and are associated with a 5-year lower limb amputation and mortality rate of 20% and 40% respectively (5). In addition, DFUs cost the NHS an estimated £1 billion per year (6).

Peripheral arterial disease (PAD) is a key risk factor in the development of DFUs (7) and is also associated with delayed DFU healing, increased risk of leg amputation and mortality (3,8). The detection of PAD in people with diabetes is fundamental though challenging. Although a variety of bedside tests are available, there is no agreement as to which is the most useful.

Review of existing evidence

Existing reviews (9,10) highlight the lack of evidence in this area. An updated systematic review and meta-analysis (11) has been performed to further evaluate the evidence for the numerous bedside tests in this cohort of patients.

MEDLINE and EMBASE databases were systematically searched for studies providing data on diagnostic performance of bedside tests used for the detection of PAD in people with diabetes. A meta-analysis was performed to obtain pooled estimates of sensitivity and specificity for the diagnosis of PAD. Eighteen studies, reporting on a total of 3016 limbs of patients with diabetes, were included in our qualitative review. Of these, 11 studies (1543 limbs) were included in the meta-analysis of diagnostic accuracy: **ABPI** (9 studies, 1368 limbs, sensitivity 63.5% [95% CI 51.7-73.9%], specificity 89.3% [CI 81.1-94.2%]); **TBPI** (3 studies, 221 limbs, sensitivity 83.0% [CI 59.1-94.3%], specificity 66.3% [CI 41.3-84.6%]); and **visual waveform assessment** (4 studies, 397 limbs, sensitivity 82.8% [CI 73.3-89.4%], specificity 86.8% [CI 75.5-93.3%]). Overall, there was a high risk of bias across studies, most frequently relating to patient selection and lack of blinding.

TEsting for Arterial disease in Diabetes (TrEAD) study

The largest study to date has been completed comparing the diagnostic performance of tests for the presence of PAD in patients with diabetes (Clinicaltrials.gov: NCT04058626; (12,13)).

This study enrolled 305 participants, across 2 centres. The performance of index tests (ABPI, TBPI, TcPO2, pulse palpation, audible waveform (handheld Doppler) and visual waveform (handheld Doppler)) were compared to a blinded reference duplex ultrasound scan (DUS).

Alongside these commonly used bedside tests we have also evaluated the performance of an ‘enhanced’ visual waveform test that has been termed Podiatry Ankle Duplex scan (PAD-scan). PAD-scan is a new focussed DUS test that directly visualises the ankle vessels and detects more detailed waveforms. The results of the TrEAD study were consistent with the findings of our meta-analysis which suggested that visual waveform assessment may be the most promising modality. It was found that visual waveform assessment with **PAD-scan** had better sensitivity than **visual handheld Doppler** (95% vs 83%, $p<0.001$) justifying further evaluation, in a limited number of selected centres, in this proposed study. Sensitivities of other tests were: **audible Doppler** (74%), **TBPI** (60%) and **ABPI** (60%). **Pulse palpation** and **TcPO2** had low sensitivities of 43% and 31% respectively, justifying exclusion from this

proposed study. Combining ABPI and pulse palpation with audible Doppler (sensitivity 84%, specificity 46%) or visual Doppler (sensitivity 87%, specificity 44%) improved sensitivity when compared to each test used in isolation. However, their combined performance was still inferior to the PAD-scan.

Cost-effectiveness of bedside tests

The cost-effectiveness of the bedside tests evaluated in the TrEAD study (14) has been estimated. A Markov model was constructed to estimate the health outcomes and costs over 5 years of different testing strategies applied to a cohort of patients with diabetes presenting to a hospital diabetic foot clinic where the prevalence of PAD and DFU was 66% and 40%, respectively. Health outcomes were incidence of new DFU, major cardiovascular events, lower limb amputation, death and DFU healing rates. Costs included those of the index tests plus further interventions as recommended by clinical guidelines.

It was found that **visual handheld Doppler** was the most cost-effective test. However, when including **PAD-scan** as part of the analysis then this dominated other options with an ICER of £11 391 per QALY. Its use would result in a reduction of the number of amputations by 24% and cardiovascular deaths by 10% over 5 years, as compared to TBPI (the next best alternative). PAD-scan had the highest probability (78.7%) of having the greatest net benefit at a willingness to pay threshold of £20 000 per QALY. PAD-scans superiority in ICER occurred at a PAD prevalence threshold of 24%.

Limitations of existing evidence

There are a number of important limitations relating to currently available evidence, which we aim to address in this proposed study.

- **Patient selection-** No single study has represented the full spectrum of patients with diabetes seen in primary and secondary care.
- **Index and reference tests-** Index tests were performed by experts whose experience may not represent the general workforce. All studies have used DUS as the reference test, which may be less reliable in interrogating the commonly affected distal vessels in diabetes (15,16) as compared to CTA or MRA.
- **Analysis by limb-** Most studies evaluated diagnostic performance by performing bilateral scans and interpreting results in each limb independently. This is a potential source of bias as the presence of PAD in one limb increases the probability of PAD being present in the other.
- **Visual waveform assessment-** A significant arterial lesion results in morphological change in the waveform detected in the downstream circulation. Although visual waveform assessment has been shown to be a promising modality there is currently no agreed definition of an ‘abnormal’ waveform. Waveform morphology exists on a spectrum according to the severity of disease; triphasic (normal), biphasic, and monophasic (abnormal). For the diagnosis of PAD, some studies use a monophasic cut-off (17,18) whilst others use a biphasic waveform as the threshold for diagnosis (19). The TrEAD study showed that overall test accuracy can be improved by using an **enhanced definition** for defining abnormal waveforms (13). This involves identifying biphasic waveforms with adverse morphological features i.e., spectral broadening, infilling of the spectral window, long forward flow or slow systolic rise time. This enhanced definition improved sensitivity as compared to the traditional monophasic waveform

threshold (95% vs 77%), and improved specificity as compared to the biphasic waveform threshold (77% vs 21%). However, a potential limitation of the TrEAD study was that visual handheld Doppler assessment may have been disadvantaged by not using this enhanced definition, which was only evaluated for the PAD-scan. In this proposed study this enhanced definition, which has been shown to be superior, will be used as the primary diagnostic threshold for visual waveform assessment.

Why this research is needed now

This research is of significant priority given the rising global prevalence of PAD (20) and diabetes (21) which will increase the burden of diabetic foot disease and place further pressures on healthcare services. Missed diagnosis of PAD is common (22), and is an important cause of avoidable amputations (22–24). Our health economics modelling has demonstrated that improvements in the detection of PAD are not only cost-effective but also may considerably reduce the number of lower limb amputations and cardiovascular deaths by enabling clinicians to optimise treatment. This will help mitigate the expected rise in disease prevalence.

The TrEAD study (13), our meta-analysis (11) and cost-effectiveness study have identified visual waveform assessment as a putative front runner. We have also demonstrated that a new enhanced definition for waveform interpretation and a new enhanced visual waveform test (PAD-scan) may further improve diagnosis. These novel findings may deliver significant and meaningful impact but require further validation (13).

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

To determine the diagnostic performance of index tests (audible handheld Doppler, visual handheld Doppler, ABPI, exercise ABPI and TBPI) for the diagnosis of PAD in patients with diabetes as determined by a reference test (CTA or MRA).

2.2 Secondary Objective

- To determine the cost-effectiveness of tests over a time horizon of 5 years
- To determine the performance of tests using exploratory diagnostic thresholds
- To explore the effect of combining different tests on diagnostic performance
- To evaluate patient acceptability of tests
- To evaluate the effect of confounding patient characteristics (e.g., neuropathy and ulceration) on diagnostic performance
- To evaluate the performance of tests for establishing the severity of PAD
- To evaluate inter- and intra-rater reliability of tests
- To evaluate the performance of PAD-scan (in selected centres).

2.3 Primary Endpoint

- Sensitivity of index tests

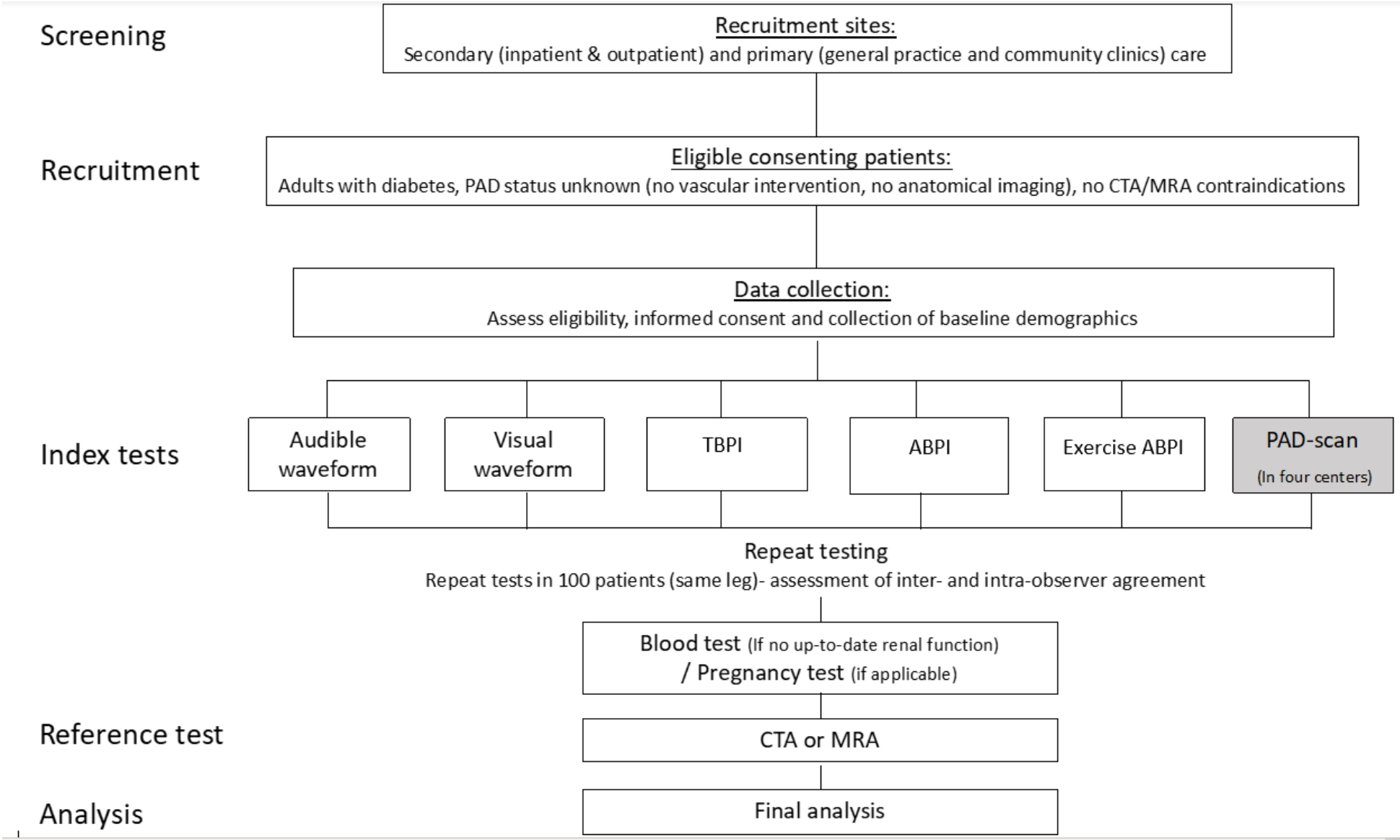
2.4 Secondary Endpoints

- Specificity, likelihood ratios, predictive values and diagnostic odds ratio.
- Health economic outcomes: 1) Cost of the test, including direct costs and amortisation of capital equipment and use of other healthcare resources for prevention and treatment of the disease over a time horizon of 5 years 2) Quality Adjusted Life Years at 5 years. 3) Incremental cost-effectiveness ratio at 5 years
- Patient acceptability
- Technical success
- Inter- and intra-rater reliability: The first 100 volunteering patients will be consented to have index tests repeated by the same operator and by an alternative operator on the same leg.

3. STUDY DESIGN

This is a prospective comparative diagnostic accuracy study. The study will be performed at 18 investigational sites in the United Kingdom. **Figure 1** is a flow chart summarising the study design.

Figure 1. Study flow chart



4. PARTICIPANT ENTRY

4.1 Study setting and population

This study is open to all patients at the participating sites with a diagnosis of diabetes meeting specific inclusion and exclusion criteria. Potential participants will also be identified by community settings who will serve as participant identification centres.

Our inclusion/exclusion criteria reflect two relevant NICE guidelines:

- Diabetic foot problems: prevention and management **(NG19)-** all adults with diabetes should undergo a foot examination (*a critical element of which is PAD testing*) at least annually, on admission to hospital and if any foot problems arise (25).

- Peripheral arterial disease: diagnosis and management **(CG147)-** Assess people for the presence of PAD if they have diabetes, non-healing wound on the legs or feet or unexplained leg pain. This guideline also makes recommendations not specific to diabetes i.e. assess people for the presence of PAD if they have symptoms, are being considered for intervention to the leg or foot, or if they need to use compression hosiery (26).

As reflected in both of these guidelines all adults with diabetes require PAD assessment at least annually. The clinical presentation of PAD may be more subtle in patients with diabetes who often suffer from accompanying peripheral neuropathy and are more likely to suffer from distal atherosclerotic disease (16). Therefore, symptoms may be absent or atypical. For this reason, inclusion to symptomatic patients has not been restricted.

Recruiting patients from all relevant healthcare settings (primary & secondary care) ensures that the full spectrum of patients with diabetes referred to in NICE guidance are represented. This includes patients 1) presenting for routine foot checks, 2) with active diabetic foot problems who may need intervention (e.g., local debridement or surgery), and 3) admitted to hospital. Recruitment from these healthcare settings also ensures sample populations with varying PAD and DFU prevalence and severity.

(i) Inclusion criteria

- Aged ≥18 years
- Known history of diabetes

(ii) Exclusion criteria

- PAD status known on imaging- prior knowledge may bias index tests.
- Known history of PAD intervention- prior knowledge may bias index tests.
- CTA and MRA contraindications- renal impairment, pregnancy, contrast medium hypersensitivity/allergy, non-compatible implants (MRA only).
- Interim surgical interventions (occurring in the time interval between index and reference tests) will be considered a protocol violation and patients will be excluded.
- Unable to provide appropriate informed consent.

5. PROCEDURES AND MEASUREMENTS

Primarily to evaluate five index tests (ABPI, exercise ABPI, TBPI, visual handheld Doppler and audible handheld Doppler). In four centres, the PAD-scan will be evaluated as a sixth test. All participants will have index tests performed in clinic (or on the ward if patient is admitted to hospital), during visit 1, by a member of the local clinical team, so that results are generalisable.

Participants will then have a reference scan (CTA or MRA) performed in a 2nd visit which will take place within 6-weeks of visit 1. In preparation for this, patients will require an up-to-date blood test to assess renal function and a pregnancy test (if applicable). The blood test may be performed at an additional visit at some centres.

5.1 Identification and recruitment of participants

Adult patients with diabetes presenting at the recruiting site will be identified by the direct healthcare team. If the patient indicated to the direct healthcare team, that they are willing to speak to the research team, the direct healthcare team will notify the research nurse or delegated individual to approach the participant with an information leaflet. This may be in person in the clinic, or by a patient invitation letter sent by mail / email or by telephone contact. They will be told that formal consent will be taken at visit 1 if they agree to partake in the study and that if they choose not to then this wouldn't affect their usual clinical care.

If necessary, non-English speaking participants will be provided with translations of study information and assistance from local NHS translation services will be obtained as per standard clinical practice.

Recruitment will be primarily from vascular, diabetic foot and general practice clinics as well as inpatient wards. Inpatients will be first identified by the direct care team (inpatient podiatry, vascular or diabetes teams) who will seek permission from the patient before any information is passed or approach made by the research team.

Potential participants will also be identified from community settings who will act as participant identification centres (PICs). These PICs will conduct a search of the patient record database and suitable participants will be contacted either via letter, mailout or SMS to inform them about the study. Interested participants would contact the study team directly for more information.

Posters placed in participating research centres will support recruitment by signposting patients to the relevant research teams. Patients can also be identified using mailout, advertisements through diabetes support networks, social media and local radio stations. With permission of the participant the reasons for non-inclusion will be logged anonymously along with a minimum data set of age and reason for exclusion. The anonymised pre-screening logs will be transferred to the Trial Coordinating Centre for the purposes of monitoring recruitment as suggested by the funding (NIHR) panel.

5.2 Screening evaluations

On visit 1, which coincides with a routine/planned visit, informed consent will be obtained before the participant undergoes any screening procedures.

5.3 Visit Schedule

	Screening	Planned/ routine visit	Blood test (in some centres)	Reference scan
Visit number	**0**	**1**	**1b**	**2**
Screening	X			
Study information material	X			
Informed consent		X		
Inclusion & exclusion criteria		X		
Demography		X		
Medical history		X		
Quality of life questionnaire (EQ-5D-5L)		X		
Index tests		X		
Repeat of index tests (same operator)*		X		
Repeat of index tests (alternative operator)*		X		
Blood test/ pregnancy test		X	(X)[ł]	
Reference scan (CTA/MRA)				X

*****Repeat tests will only be performed in the first 100 volunteering patients.
[ł]The blood test to assess renal function may require a separate, additional visit at some centres.

5.4 Follow-up

Patients will also be consented separately for permission to follow up their clinical progress through accessing their electronic health records (as part of a potential separately funded future study). Data will be collected at 12 months following visit 1 regarding DFU healing, new or recurrent ulceration, amputation (minor and major) and revascularisation.

5.5 Blood and pregnancy tests

All patients require a recent blood test to assess their renal function (Creatinine and eGFR) prior to the reference scan. This may require a separate, additional visit at a different site. Additionally, female patients of reproductive age will require a negative pregnancy test prior to the reference scan. These tests will be conducted and interpreted according to local protocol.

5.6 Data collection

A screening log will identify all approached patients and reasons for non-participation.

- Demographics: age, gender, equality and diversity information, diabetes type, history of smoking, retinopathy, chronic kidney disease, ischaemic heart disease, stroke and heart failure
- Foot history: PAD symptoms, previous history of DFU or amputation
- Foot examination: neuropathy, presence of DFU, DFU severity using the WIfI classification system (27)
- Quality of Life questionnaire: the validated EuroQoL (EQ-5D-5L) questionnaire will be used to assess the generic QoL at visit 1.
- Technical success of index tests: inability to perform, refusal and discontinuation of tests will be documented
- Results of index tests
- Evaluation of patient acceptability: patients will be asked to rate their experience of each test on a Likert scale (**Appendix**)

5.7 Index tests

Tests will be performed on one limb; the most problematic side in symptomatic patients or randomly selected side in asymptomatic patients. Tests and equipment will be standardised, and team members will undergo protocol training.

Test order

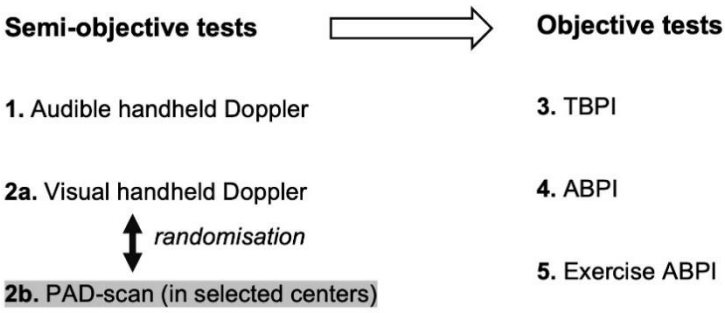
Ideally, test order (**Figure 2**) would be randomised to minimise influence carrying over from one test to the other. However, the audible and visual waveform tests involve semi-objective interpretation and therefore could be influenced by knowledge of the tests with an objective output (TBPI, ABPI and exercise ABPI). The study team believes it is better to conduct the semi-objective waveform tests first followed by the fully objective tests. Randomising the order of tests in these two blocks is not possible:

- **Semi-objective tests-** audible waveform is less objective than visual waveform assessment and so should be performed first. However, in selected centres two forms of visual waveform assessment (handheld Doppler and PAD-scan) are to be evaluated. The order of these two tests will be randomised (via REDCap) in these selected centres.

- **Objective tests-** TBPI should be performed before ABPI as it could be influenced by reactive hyperaemia secondary to proximal cuff inflation. Also, exercise ABPI should be performed last as exercise can influence all other tests.

The order of tests is summarised in **Figure 2**.

Figure 2. Order of Index tests.



Conducting index tests

Prior to the conducting the first index test participants will be rested in the supine position for at least 10 minutes with room temperature maintained between 23°C and 25°C.

- **ABPI**

ABPI measurements will be performed using a sphygmomanometer cuff placed at the ankle and a handheld audible CW Doppler device (Dopplex D900 Audio only Doppler, Huntleigh Healthcare Ltd., Cardiff) to measure dorsalis pedis and posterior tibial artery systolic pressure. Brachial artery pressures from both arms will be taken and the highest reading used to calculate the ABPI.

- **Exercise ABPI**

Exercise ABPI traditionally requires a treadmill. This limits its use in primary care, where a treadmill is not available. Additionally, the results of the patient and public involvement (PPI) work suggest that 43% of patients will not be able to walk on a treadmill (due to disability, frailty or DFU) and that an additional visit to a vascular laboratory for this test would not be acceptable. To ensure patient acceptability, repetitive heel raising will be used. This can be performed in clinics, has excellent correlation with treadmill testing (28,29) and has been advocated by the American Heart Association (30). Our PPI focus group considered this test acceptable.

The exercise ABPI protocol, will consist of 50 consecutive repetitions of active dorsiflexion whilst standing (28). The knees should be kept fully extended. Participant will be allowed fingertip support against a wall to assist with balance. The protocol will be symptoms limited, so that premature termination of exercise will be permitted if the subject experiences lower limb discomfort, chest pain, shortness of breath or feels unwell for any other unspecified reason. Instances of premature termination, and accompanying reasons, will be recorded. ABPI will be measured using the same methodology as outlined above.

In some patients, exercise ABPI may not be possible due to deformities of the foot, e.g., those with forefoot amputation, Charcot foot syndrome and forefoot plantar ulceration. Foregoing exercise ABPI will be left to the clinical teams discretion. Reasons for foregoing exercise ABPI will be documented.

- **TBPI**

Measurements will be made using the Huntleigh toe pressure kit (Huntleigh Healthcare Ltd., Cardiff) employing an infrared sensor placed on the hallux.

Brachial artery pressures from both arms will be taken and the highest reading used to calculate the TBPI.

- **Audible handheld Doppler**

Audible CW Doppler interrogation of the dorsalis pedis and posterior tibial artery (Dopplex D900 Audio only Doppler, Huntleigh Healthcare Ltd., Cardiff).

- **Visual handheld Doppler**

Visual CW interrogation of the dorsalis pedis and posterior tibial artery using the handheld Huntleigh Digital Dopplex device (Huntleigh Healthcare Ltd., Cardiff). The pseudonymised visual blood flow waveforms will be saved and may be used for future analysis.

- **PAD-scan (in selected centres)**

The PAD-scan will be performed using a portable ultrasound system (Mindray M7; Shenzhen, China) with a linear 6-14Hz transducer. The anterior tibial and posterior tibial artery will first be visualised at the ankle, using B-mode imaging and colour Doppler, in transverse and then longitudinal planes. Arterial spectral waveforms will then be sampled from the centre of each vessel 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.

Repeating index tests

The first 100 volunteering patients will have tests repeated on the same day by the same operator and also by another, blinded, operator for the assessment of intra- and inter-rater reliability. Tests will be performed using the same descriptions outlined above. A minimum of 10 minutes rest must be provided to the patient prior to each batch of tests to avoid influence from previous tests carrying forward.

5.8 Reference test

Digital subtraction angiography (DSA) is considered the gold standard for the diagnosis of PAD. However, it is invasive and carries risk. Given the previously mentioned limitations of DUS our reference test will be CTA or MRA. Both have excellent accuracy compared to DSA (31,32). Some of our centres use only CTA, whereas others use only MRA. Additionally, some patients in our PPI survey reported that they would not take part if CTA was necessitated and suggested the inclusion of MRA as an alternative.

Reference tests (CTA/MRA) will be performed according to a standardised protocol within 6-weeks of index tests. The reference test may be performed at a different participating site to that of visit 1. The final decision regarding whether the patient undergoes CTA or MRA will depend on local protocol and patient choice. Details of reference scan protocols

can be found in the **Appendix**. PAD is a chronic atherosclerotic condition and we do not envisage that there will be any change in disease status or reference test results over a short 6-week period. Interim surgical interventions (occurring in the time interval between index and reference tests) will be considered a protocol violation and patients will be excluded.

Scans will initially be reported locally and then re-reported centrally by a blinded consultant radiologist at our core lab (University Hospitals of Leicester NHS Trust). Scans will be reported locally for identification of incidental abnormal clinical findings. Local reports will not be used as part of the study analysis. To assess inter- and intra-rater reliability in the core lab, 15% of scans will be re-reported by our core lab radiologists.

Scans will be assessed using a validated angiographic scoring system (ANGIO score) (33); 10 major arteries supplying the lower limbs are each scored according to the degree of stenosis (0, 0-49% stenosis; 1, non-occlusive stenosis of ≥50%; 2, complete occlusion). The presence of one or more arterial lesions of ≥50% stenosis will be used as threshold for the diagnosis of PAD. Tandem lesions with a combined value of ≥50% will also be considered positive for PAD as they are haemodynamically significant and in certain scenarios (e.g., non-healing DFU) may prompt treatment. PAD severity will also be categorised according to the ANGIO score, as mild (≤4), moderate (5-9) or severe (≥10). These categories have been shown to correlate with risk of amputation and cardiovascular events (33).

5.9 Incidental findings

Incidental findings may potentially be identified on the reference scan (CTA or MRA). As detailed in section 5.6, all reference scans will be reported locally for identification of incidental abnormal clinical findings. These will be reported to the local clinical team and the GP.

Incidental findings may also potentially be identified on blood (e.g., kidney disease) and pregnancy tests. These will similarly be dealt with by reporting to the local clinical team and the GP.

6. INTERVENTION

6.1 Permanent Discontinuation of Study Intervention and Withdrawal from Study

(i) Permanent discontinuation of study intervention

Participants may discontinue study intervention for the following reasons:

- At the request of the participant.
- Adverse event/ Serious Adverse Event
- If the investigator considers that a participant's health will be compromised due to adverse events or concomitant illness that develop after entering the study.

(ii) Withdrawal from Study

Withdrawal from the study refers to discontinuation of study intervention and study procedures and can occur for the following reasons:

- Participant decision
- Loss to follow-up

- Subject loss of capacity

(iii) Procedures for Withdrawal from Study

There are no criteria for withdrawal from the study. Patients will be free to withdraw from the study without any effect on their usual medical care. The reason for their withdrawal will be recorded in the CRF/eCRF and medical records if offered. All randomised participants will be followed up to 12 months unless they specifically asked to be withdrawn as per intention to treat. In line with this analysis patients lost to follow up or withdrawn from the study will not be replaced.

(iv) Procedures for Withdrawal from Study due to loss of capacity

If a patient loses capacity after consenting to take part in the study, the local Principle Investigator may decide it is in the patient's best interests to be withdrawn. Any identifiable data already collected with consent will be retained and may be analysed, but no further data will be collected or any other research procedures carried out on or in relation to the patient.

7. SAFETY REPORTING

7.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical trial participant. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, whether or not considered related to the trial protocol.

For the purposes of the study, only AEs related to study procedures will be recorded.

7.2 Adverse Event recording

For the purposes of the study, all AEs will be followed up according to local practice until the event has stabilised or resolved, whichever the sooner is. It is essential that all AEs that occur during the course of the study are appropriately reported in order to ensure the participants continuing safety. Of particular importance is the assessment of any event for *causality* and *expectedness* in relation to the device.

(i) Severity of Adverse Events

Definitions for assessment of severity:

Mild: Awareness of event but easily tolerated
Moderate: Discomfort enough to cause some interference with usual activity
Severe: Inability to carry out usual activity

(ii) Causality of Adverse Events

Definitions for assessment of causality:

Unrelated: No evidence of any causal relationship
Unlikely: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial

medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).

Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).

Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

7.3 Serious Adverse Events (SAE)

(i) Definition of SAE

An SAE is defined as any event that

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

* "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.
** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

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

7.4 Reporting of SAEs

Rapid reporting of all SAEs i.e. within 24 hours, occurring during the study must be performed as detailed in SAE reporting instructions. If the investigator becomes aware of safety information that appears to be related to the trial, involving a subject who participated in the study, even after an individual subject has completed the study, this should be reported to the Sponsor.

Contact details for reporting SAEs

RGIT@imperial.ac.uk

CI email (and contact details below)

Professor Alun Davies

Please send any paper SAE forms to: DM-PAD@imperial.ac.uk

Tel: 0203 311 5208 (Mon to Fri 09.00 – 17.00)

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality.

Reporting of SAEs and review by the CI will be via the trial data collection system (CRF/eCRF).

SAEs that are related and unexpected will be reported to the RGIT as soon as possible after becoming aware of the event.

(i) **Related SAEs**

Related: resulted from administration of any of the research procedures

(ii) **Unexpected SAEs**

Unexpected: type of event is not listed in the protocol as an expected occurrence

(iii) **Reporting of SAEs that are related and unexpected**

SAEs that are related and unexpected should be notified to the relevant REC and the Sponsor in accordance with local requirements.

(iv) **Follow up of patients who have experienced a related and unexpected SAE should continue until recovery is complete or the condition has stabilised. Annual reporting of Serious Adverse Events**

Annual Progress reports will be submitted to the Sponsor and the Ethics Committee in accordance with local requirements.

7.5 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

8. STATISTICAL ANALYSES

8.1 Sample Size and power considerations

Summary of sample size calculations

Assuming PAD prevalence of 50%, with 255 with PAD and 255 without PAD, the study will have 90% power to estimate an assumed sensitivity (or specificity) to a precision of the half width of the 95% confidence interval of 8.2%. For a sensitivity (or specificity) of 80% this half width would increase to 10.2%. The level of significance was set at 1% to adjust for the 5 tests and ensure the overall level of significance does not exceed 5%. Power calculations used R.4.0.0 power.diagnostic.test in package MKmisc. The sample sizes for estimating likelihood ratios will also be estimated.

In the TrEAD study, PAD prevalence was 66%. As there will also be recruitment from primary care, with a lower PAD prevalence (34), the estimate to reflect the findings of our systematic review have been adjusted; prevalence of 50% across 18 studies (11). In TrEAD, TBPI could not be performed in 20% of patients. A similar proportion may be unable to tolerate exercise ABPI. It is estimated that 10% of patients may drop out prior to the reference test. Therefore, the sample size has been inflated by the cumulative missingness across all groups (30%) to be certain of having enough power for each and every test comparison. Thus, we aim to recruit a total of 730 patients.

Details of sample size calculations

We used R.4.0.0 routine power.diagnostic.test in package MKmisc to calculate 90% power at a notional 5% level of significance for both the sensitivity and specificity. If we assumed a 90% sensitivity (or specificity) we need 510 evaluable participants (which at 50% prevalence would be 255 with PAD, and 255 without PAD). This would allow the sensitivity (or specificity) to be calculated to within ± 8.2% (the half-width of the 95% confidence interval). For a lower assumed sensitivity (or specificity) of 80% this would increase to ± 10.2%. The estimated precision will also be calculated given these numbers for other diagnostic performance statistics such as the positive and negative predictive values, and the positive and negative likelihood ratios.

Sample size calculations for inter- and intra- rater reliability

In terms of sample size, an indicative calculation shows that using McNemar's paired test on correlated proportions, with 100 participants, with no loss to follow up, the study would have 90% power at a 5% level of significance to detect a difference of 0.17 in the discordant results (positive – negative vs. negative – positive) between two tests (e.g. 0.22 positive-negative vs. 0.05 negative-positive).

8.2 Planned recruitment rate

Accounting for holidays and unforeseeable circumstances (in a COVID-19 era) we originally allowed for 12-months to recruit 730 patients. This equates to 61 patients per month across 18 centres i.e., 3 to 4 patients per month/centre. We believed this is feasible given that the TrEAD study recruited 20 patients per month/centre and estimates from our centres indicate a minimum recruitment rate of 8 patients per month/centre. Recruitment was extended for an additional 12 months following an NIHR monitoring meeting on 17th February 2023 as the original projected targets were not met.

8.3 Internal pilot

A stop-go assessment of recruitment feasibility will be included after a 4-month internal pilot. The 18 sites will be set up in 4 months – 4 in month -1 (before the recruitment period starts, in calendar month 6 of the study), 4 in month 1, 6 in month 2, and the remaining 4 in month 3. Allowing a fallow month for holidays, 4 per centre per month will need to be achieved to reach the target sample size of 730 in 18 sites in 12 months. Recruitment feasibility will be assessed at the end of month 4, when 136 participants should have been recruited. If under 90 or fewer have been recruited, the study may be stopped (Red); between 90 and 114 adapt (more sites and/or more time – AMBER) and if 115 or more continue unchanged (GREEN – within sampling variability of our target). This will be discussed with the TSC and the funder.

8.4 Statistical Analysis

The five individual tests (and the sixth exploratory test in four sites) will be compared against the reference test (CTA/MRA), calculating standard diagnostic accuracy metrics of sensitivity, specificity, predictive values, likelihood ratio, and diagnostic odds ratio (using the bivariate model approach implemented in R). 95% confidence intervals calculated at 99% to adjust for the five comparisons will be presented. The robustness of the findings to any observed patterns of missing data will be assessed, which are expected to differ by test. A multiple imputation approach will be used assuming the data are missing at random. In addition, and probably more consistent with the likely missing data generating mechanisms, sensitivity type analyses assuming the data are missing not at random (i.e. informatively missing) will be explored. This would attempt to identify different types of missing data by an underlying reason or reasons, and then imputing values that capture plausible measurements for those missing data. The ?-adjustment approach given by van Buuren will be followed (Flexible Imputation of Missing Data, Chapman and Hall, 2018, section 3.8ff), and also the recommendations of Molenburghs & Kenward (Missing Data in Clinical Studies, Wiley, 2007; Section 19ff on sensitivity analyses). These approaches would allow the set of reasons for missing values to vary across the tests. The purpose is to stress the calculated findings to test their robustness to the observed patterns of missing data.

The subgroups of disease severity (both clinically and radiologically defined as detailed below) will be explored and those with/without neuropathy or DFU. The subgroups in the Statistical Analysis Plan will be pre-specified. Any further subgroup analysis (e.g. if suggested later by new data external to the study) will be labelled exploratory. Pre-specified subgroup analyses will be unlikely to be adequately powered. Clinical severity will be graded according to the severity of symptoms (from least to most severe; asymptomatic, intermittent claudication, rest pain and tissue loss). Severity will be measured radiologically using the ANGIO-score as outlined in section 5.7. Both will be analysed as pre-specified subgroup analyses in the Statistical Analysis Plan.

Combinations of tests will be explored to see if using more than one test has incremental diagnostic value. The combinations of tests that were clinically felt to potentially offer an improvement over individual tests will be pre-specified in the SAP, and then, acknowledging the paired data, use the approach of Pepe and Thomson (Biostatistics, 2000; 1, 2; 123-140 'Combining diagnostic test results to increase accuracy'), which looks at linear combinations of the underlying tests. Post-hoc checks will be made if there were combinations that were not pre-specified that performed even better, as hypotheses for subsequent evaluation.

It is important to quantify the ability of each of the 5 index tests to measure consistently the same measurement of interest on the same leg of the same subject using the same test kit in the same location and the same environmental conditions, within a short period of time. This quantification of the intra-rater repeatability (or reproducibility) will be undertaken using the test-retest approach (35,36). The inter-rater reliability (the agreement between two or more clinicians measuring the same subject, again as under the conditions above) using appropriate methodology (35,36) will be quantified. For the inter- and intra-rater repeatability, we will aim for a sample size of 100 per pair of index tests.

These reliability studies will be performed at the start of the study and analysed as soon as the data are mature. If an index test has unacceptable intra-rater repeatability, or unacceptable inter-rater reliability, it could be dropped from further consideration, following discussions with the independent TSC. Unacceptable intra- and inter-rater reliability will be assessed in two ways— first, in an absolute sense, by looking at the kappa statistics and using the published guidance as to what an acceptable magnitude is (Fleiss, J.L. (1981). *Statistical methods for rates and proportions* (2nd ed.). New York: John Wiley) with a kappa of <0.4 considered unacceptable. This is not unanimity over interpreting the magnitude of kappa statistics, so our second approach will compare the kappa statistics across the tests, and label unacceptable any tests that are substantially worse than the other tests.

Inter- and intra-rater reliability will also be assessed for the reporting of reference tests using the methods outlined above. Reference tests will not be repeated due to feasibility and ethical considerations.

Full details of the methods and justification of the sample sizes will be included in the comprehensive Statistical Analysis Plan, authored by the study statistician and agreed by the independent TSC. The Statistical Analysis Plan will be prepared and finalised prior to database lock.

Index test diagnostic thresholds

The performance of the index tests based on prespecified diagnostic thresholds for PAD will be evaluated. These thresholds have been selected as they demonstrated optimal diagnostic performance in the TrEAD study or are commonly used in clinical practice. However, other thresholds have been described in the literature and there is no consensus as to which are best. Therefore, different 'exploratory' thresholds will be evaluated as part of our secondary analyses. Tests generating continuous results (ABPI, TBPI and exercise ABPI) will be evaluated for performance based on optimised thresholds derived from Receiver Operating Characteristics (ROC) analysis. A 'net benefit' approach will be used (as a sensitivity type analysis over a range of plausible thresholds) following ideas for assessing the clinical utility of prognostic models summarised in Riley R et al (*Prognostic Research in Health Care; 2018; Oxford; section 7.4.3 page 168-170*). From this, it should be possible to integrate cost-effectiveness parameters into assessing the best threshold.

Diagnostic thresholds:

- o Visual waveform assessment- monophasic or biphasic waveforms with adverse features.
- o Audible waveform assessment- monophasic waveform
- o ABPI- ≤0.9 in either vessel
- o TBPI- <0.75 in either vessel
- o Exercise ABPI (31)- Post exercise ABPI ≤0.9 in either vessel.

Health economics analysis

A literature review will be conducted to identify published health economic studies in similar patient groups. Cost-effectiveness of the tests will be estimated using Markov models that simulate clinical events in a cohort of hypothetical patients with diabetes over 5 years. The structure of the model may follow that developed in previous work by this group (reference 14). Depending on their PAD status (PAD or no PAD), and ulceration status at presentation (DFU or no DFU), patients will be allocated into one of eight initial states following a test: True positive (with and without DFU), true negative (with and without DFU), false positive (with and without DFU), or false negative (with and without DFU).

True and false positive patients without DFU will be prescribed orthotics and additional foot checks, in addition to standard care. True and false positive patients with DFU will undergo confirmatory DUS, and, if confirmed positive, angiography, revascularisation and low dose rivaroxaban, in addition to standard care. True and false negative patients will continue with standard care for the remainder of the 5 year time horizon. The accuracy of test outcomes will be obtained from the study. The probability of clinical events (new DFU incidence and healing rates of DFU, amputation of unhealed limbs, cardiovascular events and death) and treatment effects associated with recommended interventions for diagnosed PAD patients (e.g., orthotics, revascularisation, rivaroxaban) will be obtained from NICE evidence reviews and the literature. The study will be conducted from the perspective of the UK NHS and Personal Social Services according to NICE methodological guidelines and reported according to CHEERS standards. Costs, QALYs, ICERs and measures of uncertainty over 5 years will be estimated. Tests costs will be estimated by bottom-up costings during the course of the study that will include machine capital acquisition cost and one-off training (amortised over the useful life and expected through-put of patients per year), consumables and operator time. Prices and unit costs of items will be obtained from manufacturers and national databases.

9. REGULATORY, ETHICAL AND LEGAL ISSUES

9.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the 2013 revision of the 1964 Declaration of Helsinki.

9.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

9.3 Research Ethics Committee (REC) Approval

(i) Initial Approval

Prior to the enrolment of participants, the REC must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Participant Information Sheet and Consent Form, any other written information that will be provided to the

participants, any advertisements that will be used and details of any participant compensation.

(ii) Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval as instructed by the Sponsor. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

(iii) Annual Progress Reports and End of Trial Notification

The REC will be sent annual progress reports in accordance with national requirements and will also be informed about the end of the trial, within the required timelines.

9.4 HRA approval

Health Research Authority (HRA) approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing.

The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

9.5 Other Required Approvals

The procedures are compliant with the Ionising Radiation (Medical Exposure) Regulations, and appropriate review by a Medical Physics Expert and Clinical Radiation Expert has been undertaken.

9.6 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF/CRF and reviewed by the Chief Investigator. Protocol violations will be reported to the Sponsor.

An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.

A serious breach is defined as:

A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the UK trial participants; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the REC within 7 days of becoming aware of the serious breach.

9.7 Insurance and Indemnity and Sponsor

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

9.8 Trial Registration

The study will be registered on a trial database in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations. The study will be registered on ISCTRN.

9.9 Informed Consent

Consent will be through standard GCP measures including a patient information sheet and signed informed consent form. No minors are eligible to join DM PAD.

Consent to enter the study will be sought from each participant only after a full verbal explanation has been given, and an information leaflet offered. The consent will be informed, voluntary and participants will be given an appropriate amount of time to consider participation and to ask questions. There will be no set minimum time to consider the trial as this will be determined on a case by case basis, this is usually 24 hours but could be less if there is agreement from both the researcher and participant that the consent is fully informed.

Signed participant consent will be obtained and participants will be asked to consent for their data to be linked with appropriate databases including Hospital Episode Statistics (HES), and the National Vascular Database as well as for longer term follow-up in the event the trial is extended. A copy of the signed Participant Information Sheet/Informed Consent Form document will be provided to the patient and the original Informed Consent Form should be retained with the source documents.

The right of the participant to refuse to participate without giving reasons will be respected, although if the participant is willing a reason for declining will be recorded. After the participant has entered the trial 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 at any time from the protocol treatment without giving reasons and without prejudicing further treatment. Participants will be asked to consent to long term follow up to allow for linkage to routine datasets including Hospital Episode Statistics (HES) and the National Vascular Database.

9.10 Contact with General Practitioner

It is the investigator's responsibility to inform the participant's General Practitioner (where applicable) by letter that the participant is taking part in the study provided the participant agrees to this, and information to this effect is included in the Participant Information Sheet and Informed Consent. A copy of the letter should be filed in the Investigator Site File.

9.11 Participant Confidentiality

The investigator must ensure that the participant's confidentiality is maintained. On the CRF or other documents submitted to the Sponsors, participants will be identified by a participant ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to participants' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS, Regulatory Authorities and RECs.

9.12 Data Protection and Participant Confidentiality

The investigators and study site staff will comply with the requirements of the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

9.13 End of Trial

The end of the Trial will be defined as the last participant's last visit.

9.14 Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Participant files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

10. DATA MANAGEMENT

10.1 Source Data

Data will be written directly into the CRF (source data) and then transcribed into the eCRF. Source documents include original documents related to the trial, to medical treatment and to the history of the participant, and adequate source documentation must be maintained to allow reliable verification and validation of the trial data.

10.2 Language

CRFs will be in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by participants must use vocabulary that is clearly understood, and be in the language appropriate for the study site.

10.3 Database

Data management will be through the REDCap, a web-based data entry system that builds a database for each individual clinical trial. The Data Management Services team (based at ECTU) will work with the Investigators, Trial Manager, Trial Statisticians and Trial Teams to design and build bespoke eCRFs and validation rules for data entry to ensure the data is collected accurately and stored securely. They will also provide the appropriate user training. The Trial Manager will visit the sites to verify the quality of the data.

10.4 Data Collection

Details of procedures for CRF/eCRF completion will be provided in a study manual.

10.5 Archiving

All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 10 years following the end of the study.

11. STUDY MANAGEMENT STRUCTURE

The study will be coordinated by a trial manager who will report to the Chief Investigator. The trial manager will liaise with local principal investigators to ensure that the trial is conducted locally according to protocol and in an expeditious manner. The organisational structure and responsibilities are outlined below.

11.1 Trial Steering Committee

A Trial Steering Committee (TSC) will be convened including as a minimum an independent Chair, independent clinician, the Chief Investigators and Trial Manager. A TSC meeting will be held at the start of the study prior to commencement of recruitment and at least annually as per NIHR guidelines. The role of the TSC is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter. A lay PPI representative will be included.

11.2 Trial Management Group

A Trial Management Group (TMG) will be convened including the Chief Investigator, co-investigators and key collaborators, trial statistician and trial manager. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Meetings will be held monthly throughout the set up and recruitment phase and alternate months subsequently until trial closure. Details of membership, responsibilities and frequency of meetings will be defined in separate terms of Reference.

11.3 Data Monitoring Committee

A data monitoring committee meeting will be held prior to first patient first visit and will then be held prior to each TSC meeting. Further details will be defined in the separate DMC Charter. Statistical advice and analysis will be conducted by Professor John Norrie (ECTU), who has advised on this studies design and sample size. Professor Norrie will produce the Statistical Analysis Plan and subsequent reports for the Data Monitoring Committee

11.4 Special advisory group

As successful primary (general practice & community) care recruitment is a priority, a Special Advisory Group (SAG) chaired by two leading experts in primary care diabetes and vascular medicine (Professor Kamlesh Khunti and Professor Azeem Majeed) will be formed. Other members of the SAG include, Ms Trusha Coward (community podiatrist), Ms Joanna Pitt (primary care nurse), Ms Caroline Durack (primary care manager), Dr Patrick Holmes (General Practitioner) and Professor Ahmet Fuat (General Practitioner).The SAG will advise on the recruitment and delivery of the study outside of secondary care to ensure that patients from these healthcare settings are adequately represented. Both chairs will sit on the TMG.

11.5 Patient Advisory Group

A Patient Advisory Group (PAG) will be convened. PAG will be meet annually prior to TSC meetings to ensure that a wide range of patient perspectives are considered during the study.

11.6 Early Discontinuation of the Study

There are no formal stopping rules but safety will be reviewed periodically by the DMC who could recommend early discontinuation of the study.

11.7 Risk Assessment

A study-specific risk assessment will be performed prior to the start of the study by the study sponsor. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study.

11.8 Monitoring

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

Monitoring procedures and requirements will be documented in a Monitoring Plan, in accordance with the risk assessment.

11.9 Quality Control and Quality Assurance

Quality Control will be performed according to Imperial College internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor. All necessary data and documents will be made available for inspection.

The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care.

11.10 Peer review

This research has been reviewed by the Surgery Peer Review Board at Imperial College London, the DM PAD multicentre research group and the Collaborations Committee at Edinburgh Clinical Trials Unit. The scientific quality of the research was also reviewed and

assessed by the NIHR HTA external reviewers as part of the grant application for funding, which was subsequently awarded.

11.11 Patient and Public Involvement

The development of the proposal has been informed by patients and the public and PPI activities have been conducted in line with INVOLVE recommendations (37).

Developing the research question

An emotional mapping exercise of a group of patients with diabetes identified anxiety associated with PAD diagnosis. This helped identify and prioritise the current topic prior to this HTA call.

Learning from the experience of patients in the TrEAD study

A phone survey of 57 patients from the TrEAD study followed by a focus group discussion, led by our PPI co-applicant Elizabeth Pigott who has personal experience of diabetic foot disease and working in study steering groups was conducted. The strength of this approach is that the PPI is not centred around hypothetical discussions but incorporates the perspective of patients involved in a similar study. Furthermore, the PPI is truly inclusive as a significant proportion of patients in the TrEAD study were from BAME groups (28%) and suffered from disabilities (52%). This informed the following changes:

- Incorporating a non-treadmill exercise ABPI test (see 'Index tests').
- Advertising the study online to improve accessibility for all patients (see **'**Equality, Diversity and Inclusion')
- Providing a lay summary of individual test results with actionable recommendations, in addition to the GP letter (see 'Dissemination, engagement and projected outputs')
- Patients anticipated difficulties in accessing different parts of hospitals for blood tests and imaging, due to difficult directions and access issues for those with disabilities. After discussion it was agreed that we should work with local sites to ensure that clear written directions are made available to patients and blood tests are performed in the same place as index tests (where feasible).

Learning from the wider diabetic community

An online survey of 123 people was conducted; 96% felt the research was important. 6% indicated that they would not take part if CTA was necessitated and 10% felt the study was not easy to understand. This prompted us to make the following changes, which were accepted by our study focus group:

- Include MRA as an alternative reference imaging modality
- Incorporate information regarding CTA radiation exposure with a 'real world' comparison in our patient information sheet.
- Drafting and revising our 'Plain English Summary'

Management, analysis and dissemination

Our patient co-investigator, Ms Elizabeth Pigott will chair a Patient Advisor Group who will meet annually to ensure that a wide range of patient perspectives are considered during the

study. Other members of the Patient Advisory Group were also involved in the development of this proposal.
The Patient Advisory Group will also contribute to the interpretation of study findings, thereby allowing us to integrate patients perspectives in the analysis phase.

Results will be disseminated via NIHR INVOLVE website, social media, patient forums, blogs, podcasts and presentation at patient meetings (by Ms Elizabeth Pigott, PPI lead). Educational patient video and infographics explaining the rationale behind the study and presenting the study results will also be disseminated.

11.12 Publication and Dissemination policy

The Consort Guidelines and checklist should be reviewed prior to generating any publications for the trial to ensure they meet the standards required for submission to high quality peer reviewed journals etc. http://www.consort-statement.org/. Results will be reported according to the Standards for Reporting of Diagnostic Accuracy Studies (STARD) checklist.

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

It is understood by the investigator that the Sponsor will use information developed in this clinical study and, therefore, may disclose it as required to other clinical investigators. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed.

A Clinical Study Report summarising the study results will be prepared and submitted to the REC within a year of the end of study.

The project output will include the following:

- Healthcare providers- Results will be disseminated through **publication** (study protocol, main study results, cost-effectiveness analysis, follow-up analysis), **presentation** at conferences, **social media**, **blog posts** and **podcasts** to increase reach. A **press release** via the press offices of partaking centres will be issued. **Seminars** will be run to engage podiatrists and primary care nurses.
- Commissioners- The results will be shared with local CCGs and NICE.
- Patients- Results will be disseminated via NIHR INVOLVE website, social media, patient forums, blogs, podcasts and presentation at patient meetings (by Ms Elizabeth Pigott, PPI lead). Educational patient **video** and **infographics** explaining the rationale behind the study and presenting the study results will also be disseminated.

- Study participants- As per our PPI feedback patients will receive **lay summaries of their individual test results**. They will be kept up to date with study progress through our monthly **newsletter** which will be emailed and also made available via the **study website**. Educational video and infographics will also be circulated to study participants as per our PPI feedback.
- Study centres- Staff at study centres will be kept up to date via the monthly study newsletter.

Professional networks of all co-applicants and TSC members will be utilised for dissemination of our findings. To further maximise reach support has been gained from relevant organisations including: Diabetes UK, College of Podiatry, Circulation Foundation, The Society of Vascular Nurses, Vascular and Endovascular Research Network (VERN), The Lindsay Leg Club Foundation, Vascular Society, knowdiabetes.org.uk and The Royal Society of Medicine (Section of the Vascular, Lipid & Metabolic Medicine). We have also gained support from the London and West Midlands Diabetic Footcare Networks.

12. REFERENCES

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res Clin Pract. 2019 Nov;157:107843.
2. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis (dagger). Ann Med. 2017 Mar;49(2):106–16.
3. NHS Digital. National Diabetes Foot Care Audit Fourth Annual Report. 2019.
4. Carrington AL, Mawdsley SK, Morley M, Kincey J, Boulton AJ. Psychological status of diabetic people with or without lower limb disability. Diabetes Res Clin Pract. 1996 Apr;32(1–2):19–25.
5. Moulik PK, Mtonga R, Gill G V. Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. Diabetes Care [Internet]. 2003 Feb [cited 2016 Jun 30];26(2):491–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12547887
6. Kerr M, Barron E, Chadwick P, Evans T, Kong WM, Rayman G, et al. The cost of diabetic foot ulcers and amputations to the National Health Service in England. Diabet Med. 2019 Aug;36(8):995–1002.
7. Ince P, Abbas ZG, Lutale JK, Basit A, Ali SM, Chohan F, et al. Use of the SINBAD classification system and score in comparing outcome of foot ulcer management on three continents. Diabetes Care [Internet]. 2008 May 1 [cited 2018 Feb 12];31(5):964–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18299441
8. Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia [Internet]. 2008 May [cited 2017 Feb 26];51(5):747–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18297261
9. National Institute for Health and Care Excellence (NICE). Peripheral Arterial Disease: Diagnosis and Management. Evidence review for determining diagnosis and severity of PAD in people with diabetes. 2018.
10. Forsythe RO, Apelqvist J, Boyko EJ, Fitridge R, Hong JP, Katsanos K, et al. Effectiveness of bedside investigations to diagnose peripheral artery disease among people with diabetes mellitus: A systematic review. Diabetes Metab Res Rev. 2020 Mar;36 Suppl 1:e3277.
11. Normahani P, Mustafa C, Shalhoub J, Davies AH, Norrie J, Sounderajah V, et al. A systematic review and meta-analysis of the diagnostic accuracy of point-of-care tests used to establish the presence of peripheral arterial disease in people with diabetes. J Vasc Surg. 2020;IN PRESS.
12. Normahani P, Poushpas S, Alaa M, Bravis V, Aslam M, Jaffer U. Study protocol for a comparative diagnostic accuracy study of bedside tests used to detect arterial disease in diabetes: TEsting for Arterial disease in Ddiabetes (TrEAD) study. BMJ Open. 2020 Feb;10(2):e033753.
13. Normahani P, Poushpas S, Alaa M, Bravis V, Sounderajah V, Aslam M, et al.

Diagnostic accuracy of point-of-care tests used to detect arterial disease in diabetes: TEsting for Arterial disease in Diabetes (TrEAD) study. Ann Surg.

14. Normahani P, Epstein D, Gaggero A, Davies AH, Sounderajah V, Jaffer U. Cost-effectiveness of diagnostic tools to establish the presence of peripheral arterial disease in people with diabetes. Ann Surg. 2021;IN PRESS.
15. Eiberg JP, Grønvall Rasmussen JB, Hansen MA, Schroeder T V. Duplex ultrasound scanning of peripheral arterial disease of the lower limb. Eur J Vasc Endovasc Surg [Internet]. 2010 Oct [cited 2013 Dec 12];40(4):507–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20609601
16. Diehm N, Shang A, Silvestro A, Do D-D, Dick F, Schmidli J, et al. Association of cardiovascular risk factors with pattern of lower limb atherosclerosis in 2659 patients undergoing angioplasty. Eur J Vasc Endovasc Surg. 2006 Jan;31(1):59–63.
17. Tehan PE, Sebastian M, Barwick AL, Chuter VH. How sensitive and specific is continuous-wave Doppler for detecting peripheral arterial disease in people with and without diabetes? A cross-sectional study. Diabetes Vasc Dis Res. 2018 Sep;15(5):396–401.
18. Tehan PE, Bray A, Chuter VH. Non-invasive vascular assessment in the foot with diabetes: sensitivity and specificity of the ankle brachial index, toe brachial index and continuous wave Doppler for detecting peripheral arterial disease. J Diabetes Complications. 2016;30(1):155–60.
19. Williams DT, Harding KG, Price P. An evaluation of the efficacy of methods used in screening for lower-limb arterial disease in diabetes. Diabetes Care [Internet]. 2005 Sep [cited 2016 Jun 28];28(9):2206–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16123491
20. Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. Lancet Glob Heal. 2019 Aug;7(8):e1020–30.
21. Rathmann W, Giani G. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Vol. 27, Diabetes care. United States; 2004. p. 2568–9; author reply 2569.
22. Normahani P, Mustafa C, Standfield NJ, Duguid C, Fox M, Jaffer U. Management of peripheral arterial disease in diabetes: a national survey of podiatry practice in the United Kingdom. [cited 2018 Nov 6]; Available from: https://doi.org/10.1186/s13047-018-0270-5
23. Mills JL, Beckett WC, Taylor SM. The diabetic foot: consequences of delayed treatment and referral. South Med J [Internet]. 1991 Aug [cited 2017 Feb 21];84(8):970–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1882274
24. Diabetes UK. Fixing footcare in Sheffield: Improving the pathway [Internet]. 2015 [cited 2016 Dec 29]. Available from: https://www.diabetes.org.uk/Documents/Professionals/Professional resources/Footcare Case Study 1 - Improving the pathway in Sheffield (February 2015).pdf
25. National Institute for Health and Care Excellence (NICE). Diabetic foot problems: prevention and management | Guidance and guidelines. 2015;
26. Peripheral arterial disease: diagnosis and management | Guidance and guidelines |

NICE. [cited 2016 May 10]; Available from: https://www.nice.org.uk/guidance/cg147

27. Mills JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg [Internet]. 2014 Jan 1 [cited 2018 Dec 4];59(1):220-34.e1-2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24126108

28. McPhail IR, Spittell PC, Weston SA, Bailey KR. Intermittent claudication: an objective office-based assessment. J Am Coll Cardiol. 2001 Apr;37(5):1381–5.

29. Amirhamzeh MM, Chant HJ, Rees JL, Hands LJ, Powell RJ, Campbell WB. A comparative study of treadmill tests and heel raising exercise for peripheral arterial disease. Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg. 1997 Mar;13(3):301–5.

30. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 2012 Dec;126(24):2890–909.

31. Menke J, Larsen J. Meta-analysis: Accuracy of contrast-enhanced magnetic resonance angiography for assessing steno-occlusions in peripheral arterial disease. Ann Intern Med. 2010 Sep;153(5):325–34.

32. Met R, Bipat S, Legemate DA, Reekers JA, Koelemay MJW. Diagnostic performance of computed tomography angiography in peripheral arterial disease: a systematic review and meta-analysis. JAMA. 2009 Jan;301(4):415–24.

33. Morris DR, Singh TP, Moxon J V, Smith A, Stewart F, Jones RE, et al. Assessment and validation of a novel angiographic scoring system for peripheral artery disease. Br J Surg. 2017 Apr;104(5):544–54.

34. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA [Internet]. 2001 Sep 19 [cited 2014 Nov 10];286(11):1317–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11560536

35. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet (London, England). 1986 Feb;1(8476):307–10.

36. Altman D. Practical Statistics for Medical Research. Practical Statistics for Medical Research. Chapman & Hall/CRC; 1991. 369ff p.

37. Hayes H, Buckland S, Tarpey M. Briefing notes for researchers: public involvement in NHS, public health and social care research. National Institute for Health Research (NIHR) Involve. 2012.

13. REVISION HISTORY

Version	Date	Summary of changes
1.0	30/07/2021	First version
2.0	02/03/2022	Changes to the screening / recruitment process: patients can be approached in clinics / inpatient wards / GP practices etc. by the research team after being identified by the direct healthcare team (removing the need to contact the patient 72 hours ahead of their routine clinical appointment). Addition of a QoL questionnaire (EQ-5D-5L) at visit 1. Minor changes to wording of "diabetic patients" / "diabetic population" to "patients with diabetes". Clarification to the data set collected on the screening logs. TBPI index test – to use brachial (arm) measurements rather than from the index fingers.
3.0	04/04/2022	Change the order the index tests are performed - TBPI to be performed before ABPI
4.0	18/05/2022	At some participating centres, participants may be required to attend an additional visit for the purposes of taking blood to assess renal function (if no up-to-date renal blood test). Participants may be required to attend a different participating centre for visit 2 (reference scan) to that of visit 1. Extension of the time window between the index tests being performed (visit 1) and the reference scan (visit 2) from 2 weeks to 6 weeks.
5.0	25/07/2022	Include the option to recruit from community settings via participant identification centres (PICs)
6.0	28/02/2023	Minor wording change to clarify the recruitment period was extended for an additional 12 months in February 2023.

SIGNATURE PAGE 1 (CHIEF INVESTIGATOR)

The signature below constitutes approval of this protocol by the signatory, on behalf of the Protocol Development Group, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Diagnostic tools to establish the presence and severity of peripheral arterial disease in people with diabetes

Protocol Number: 6.0

Signed:

Usman Jaffer
Mr

Date: 28/02/2023

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Diagnostic tools to establish the presence and severity of peripheral arterial disease in people with diabetes

Protocol Number: 6.0

Signed: Keith Boland Digitally signed by Keith Boland Date: 2023.03.02 15:25:26 Z

Keith Boland

Imperial College London

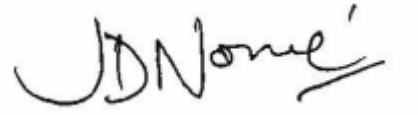
Date: 28/02/2023

SIGNATURE PAGE 3 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Diagnostic tools to establish the presence and severity of peripheral arterial disease in people with diabetes

Protocol Number: 6.0

Signed: 

_____

John Norrie
Professor
Usher Institute- University of Edinburgh

Date: 28/02/2023

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Diagnostic tools to establish the presence and severity of peripheral arterial disease in people with diabetes

Protocol Number: 6.0

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____

APPENDICES

Evaluation of patient acceptability- Likert scale

Overall, how satisfied were you with each of the tests you have had today?					
	 Very unsatisfied	 Unsatisfied	 Neutral	 Satisfied	 Very satisfied
Ankle-brachial pressure index (ABPI)					
Exercise ankle-brachial pressure index (Exercise ABPI)					
Toe-brachial pressure index					
Audible handheld Doppler					
Visual handheld Doppler					
PAD-scan (if applicable)					

CTA reference scan protocol

Peripheral CT angiograms can be obtained with all current multiple–detector row CT scanners (i.e., four or more channels). A standardised scanning protocol programmed into the scanner and the study can easily be performed in 10–15 minutes of room time. Breath holding is required only at the beginning of the CT acquisition through the abdomen and pelvis. A medium to small imaging field of view (with the greater trochanter used as a bony landmark) and a medium to soft reconstruction kernel are generally used for image reconstruction, imaging continues to the whole foot. Series 1 is imaged from Diaphragm to Ankles and then from the Knees to Ankles to achieve a delayed phase of imaging especially if there is a proximal stenosis/occlusion causing a delayed flow of contrast to the ankles. A region of interest is taken in the level of the descending thoracic aorta (DTA) or coeliac axis.

A 10–15 mm2 circular region of interest is placed inside the middle of the aortic lumen and this will subsequently measure the Hounsfield units of the aortic lumen on subsequent scanning. At 10 seconds following IV contrast administration, serial low-dose monitoring CT scans are obtained at the same table position (DTA or coeliac axis level) at 2-second intervals. When the region of interest detects a pre-set contrast enhancement level (usually a 100– 150 HU value), there is automatic triggering of the scanner to acquire images in the desired scan range, usually from the level of the celiac axis to the feet. This time-efficient method ensures optimal arterial enhancement within the region of interest. In general, 75 mls contrast is used with a chasing bolus of 100 mls Saline to produce a compact volume load.

This is injected at a rate of 4 ml/sec from a Venflon in the antecubital fossa. CT settings; kVp: 100-120, TI/pitch: 1.3/111 (fast) 0.8/27-65; FOV: 350-400(L), Rotation time: 0.35-0.5; SD: 12-12.5 (all standard sure exp), Detector configuration: 0.5x80 (depending on centres' CT scanner channel). This protocol allows reconstruction of the dataset on a 3D workstation, therefore all images will be able to be reconstructed at any plane by the reporting radiologist.

MRA reference scan protocol

MR angiography will be performed in the local hospitals scanner 1.5-3T MR. An AP phased array surface body coil will be used in conjunction with a standard receivers for signal transmission and reception. The coil is placed to cover the lower region of the abdominal portion of the aorta and included the iliac arteries to the level of the inguinal ligament.

Coverage is from the diaphragm to the foot. Depending on the centre either a test bolus of Gadolinium based contrast agent is injected via the antecubital vein or to the infrarenal region of the abdominal aorta, which combines a test bolus with a multiphase, single section, gradient recalled echo sequence. A bolus tracking method will be obtained with a ROI in the aortic lumen at the level of the coeliac axis where repeat scanning is performed, the full bolus of contrast is injected at a rate of 2-3mls/sec from a Venflon in the antecubital fossa is administered, and when the bolus is detected within the vessel, the technologist can trigger scan acquisition. The coronal oblique plane is preferred for bolus-chase MRA because it covers the largest field of view in the shortest scanning time while maintaining high spatial resolution in the slice-select direction. Subtraction techniques will be employed to improve contrast resolution in CE-MRA.

Short TR and TE for fast acquisition are accomplished with 3D spoiled gradient-echo pulse sequences. Spoiling increases the contrast-to-noise ratio (CNR) by suppressing residual background signal. As in other MR applications, the acquisition time is determined by the TR, the number of phase-encoding steps, the number of slices, the fraction of k-space sampled, and the acceleration factor (when parallel imaging is used). The gradient strength governs the shortest possible TR (< 5 milliseconds) and TE (< 3 milliseconds), although parameters such as wider bandwidth, smaller flip angles, and fractional echo can shorten the TR and TE. A flip angle of 15-45° is typically used. MRA can be acquired with either a single phase or a time-resolved MRA, depending on the centres preference. Using these sequences, it provides anisotropic images, which allows reconstruction of the dataset on a 3D workstation, therefore all images will be able to be reconstructed at any plane by the reporting radiologist.