




# BMJ Open Study protocol for a multicentre comparative diagnostic accuracy study of tools to establish the presence and severity of peripheral arterial disease in people with diabetes mellitus: the DM PAD study

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## ABSTRACT

**Introduction** Peripheral arterial disease (PAD) is a key risk factor for cardiovascular disease, foot ulceration and lower limb amputation in people with diabetes. Early diagnosis of PAD can enable optimisation of therapies to manage these risks. Its diagnosis is fundamental, though challenging in the context of diabetes. Although a variety of diagnostic bedside tests are available, there is no agreement as to which is the most accurate in routine clinical practice. The aim of this study is to determine the diagnostic performance of a variety of tests (audible waveform assessment, visual waveform assessment, ankle brachial pressure index (ABPI), exercise ABPI and toe brachial pressure index (TBPI)) for the diagnosis of PAD in people with diabetes as determined by a reference test (CT angiography (CTA) or magnetic resonance angiography (MRA)). In selected centres, we also aim to evaluate the performance of a new point-of-care duplex ultrasound scan (PAD-scan).

**Methods and analysis** A prospective multicentre diagnostic accuracy study (ClinicalTrials.gov Identifier NCT05009602). We aim to recruit 730 people with diabetes from 18 centres across the UK, covering primary and secondary healthcare. Consenting participants will undergo the tests under investigation. Reference tests (CTA or MRA) will be performed within 6 weeks of the index tests. Imaging will be reported by blinded consultant radiologists at a core imaging lab, using a validated scoring system, which will also be used to categorise PAD severity. The presence of one or more arterial lesions of  $\geq 50\%$  stenosis, or tandem lesions with a combined value of  $\geq 50\%$ , will be used as the threshold for the diagnosis of PAD. The primary outcome measure of diagnostic performance will be test sensitivity.

**Ethics and dissemination** The study has received approval from the National Research Ethics Service (NRES) (REC reference 21/PR/1221). Results will be disseminated through research presentations and papers.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Multicentre study recruiting from primary, secondary and community healthcare will make the results generalisable.
- ⇒ Pragmatic design and representative patient cohort will make the results immediately relevant to clinical practice.
- ⇒ Study design has been heavily informed by patient and public involvement, thereby improving the chance of successful recruitment and completion.
- ⇒ Reference test is not the traditional gold standard for peripheral arterial disease diagnosis (ie, intra-arterial angiography). Non-invasive, accurate cross-sectional arterial imaging will be the reference standard for this study.

**Trial registration number** NCT05009602.

## INTRODUCTION

Diabetes is a major global healthcare issue with an estimated prevalence of 9.3% (463 million people), rising to 10.2% (578 million) by 2030.<sup>1</sup> Over 6% of people with diabetes develop a diabetic foot ulcer (DFU).<sup>2</sup> DFUs are slow to heal,<sup>3</sup> have a negative impact on patient quality of life<sup>4</sup> and are associated with a 5-year lower limb amputation and mortality rate of 20% and 40%, respectively.<sup>5</sup> In addition, DFUs cost the National Health Service (NHS) an estimated £1 billion per year.<sup>6</sup>

Peripheral arterial disease (PAD) is a key risk factor in the development of DFUs<sup>7</sup> and is also associated with delayed DFU healing, increased risk of leg amputation and

mortality.<sup>38</sup> 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.

### Existing evidence

Reviews of existing evidence<sup>9–11</sup> highlight the lack of good quality evidence on this topic with a high risk of bias across studies, frequently relating to patient selection and lack of blinding.

The recently completed Testing for Arterial disease in Diabetes (TrEAD) study represents the largest study on this topic to date.<sup>12–13</sup> The results of this study suggest that visual waveform assessment may be a promising modality. Furthermore, health economics modelling of the TrEAD data suggests that visual waveform assessment is the most cost-effective test (incremental cost-effectiveness ratio (ICER) £11 391), and that its use would result in a reduction in the number of amputations by 24% and cardiovascular deaths by 10% over 5 years as compared with next best alternative.<sup>14</sup> However, these findings need to be further validated in a multicentre diagnostic accuracy study which addresses limitations relating to currently available evidence.

There are several important limitations relating to currently available evidence, which we aim to address in this proposed study. These include:

- ▶ **Patient selection:** No study has evaluated the full spectrum of the diabetic population seen in primary and secondary healthcare.
- ▶ **Index and reference tests:** Index tests in currently available studies were performed by expert staff whose experience may not represent the general healthcare workforce. All studies have used duplex ultrasound (DUS) as the reference test, which may be less reliable in interrogating the commonly affected distal vessels in those with diabetes<sup>15–16</sup> as compared with CT angiography (CTA) or MR angiography (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 what constitutes 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,<sup>17–18</sup> while others use a biphasic waveform as the threshold for diagnosis.<sup>19</sup> The TrEAD study showed that overall test accuracy can be improved by using an enhanced definition for defining abnormal

waveforms.<sup>13</sup> This involves identifying biphasic waveforms with adverse morphological features, that is, spectral broadening, infilling of the spectral window, long forward flow or slow systolic rise time. This enhanced definition improved sensitivity as compared with the traditional monophasic waveform threshold (95% vs 77%), and improved specificity as compared with 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 a new focused DUS test that directly visualised the ankle vessels (Podiatry Ankle Duplex scan; 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<sup>20</sup> and diabetes<sup>21</sup> which will increase the burden of diabetic foot disease and place further pressures on healthcare services. Missed diagnosis of PAD is common,<sup>22</sup> and is an important cause of avoidable amputations.<sup>22–24</sup> Health economic 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.<sup>14</sup> This will help mitigate the expected rise in disease (both PAD and diabetes) prevalence.

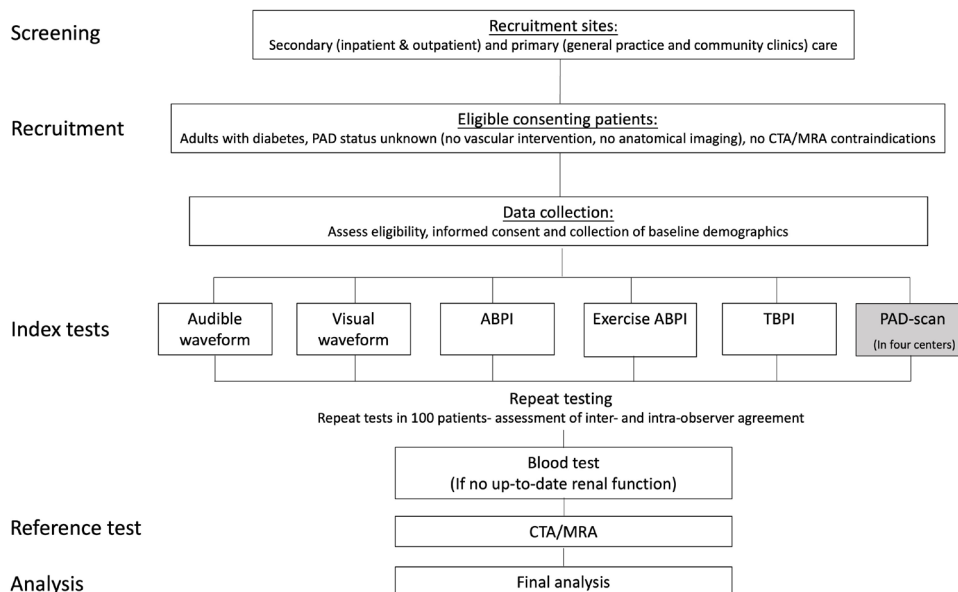
### Objectives

#### Primary objective

The primary objective of this study is 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 people with diabetes as determined by a reference test (CTA or MRA).

#### Secondary objectives

- ▶ To determine the cost-effectiveness of tests over an appropriate 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 (eg, neuropathy and ulceration) on diagnostic performance.
- ▶ To evaluate the performance of tests for establishing the severity of PAD.
- ▶ To evaluate inter-rater and intrarater reliability of tests.
- ▶ To evaluate the performance of PAD-scan (in selected centres).



**Figure 1** Study flow chart. ABPI, Ankle Brachial Pressure Index; CTA, CT angiography; MRA, MR angiography; PAD, peripheral arterial disease; TBPI, Toe Brachial Pressure Index.

## METHODS AND ANALYSIS

### Trial design

This is a prospective comparative diagnostic accuracy study. The trial schema is presented in [figure 1](#).

### Study setting

To ensure that all relevant healthcare settings are represented, we will be recruiting from community (n=2), primary (n=2) and secondary care (n=14). There will be 18 recruiting centres across the UK; London (n=4), South West (n=2), South East (n=3), East of England (n=1), East Midlands (n=1), West Midlands (n=1), Yorkshire and the Humber (n=1), North East (n=3), Wales (n=1) and Scotland (n=1).

### Eligibility criteria

The target population for this study are adults with diabetes, with or without DFU, presenting to vascular services (inpatient and outpatient), diabetic foot (community and secondary healthcare) and general practice clinics. Patients will be eligible for enrolment into the

study if they fulfil the inclusion and exclusion criteria, as defined in [box 1](#).

### Recruitment

Recruitment will be primarily from vascular, diabetic foot and general practice clinics as well as inpatient wards. The start date of the study is April 2022 and we estimate that the study will complete within 12 months of commencement. This equates to 61 patients per month across 18 centres, that is, 3–4 patients per month per centre.

Adults with diabetes will be prescreened by a member of the direct care team. If eligible for recruitment and willing to speak to a research nurse. If willing, the study will be explained and if the patient gives verbal consent to receiving study information material (online supplemental appendix 1), these will be provided on visit 1, 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 would not affect their usual clinical care. On visit 1, informed consent (online supplemental appendix 1) will be obtained before the participant undergoes any screening procedures. Following this, data will be collected and index tests completed. The visit schedule is summarised in [table 1](#).

### Data collection

A screening log will identify all approached patients and reasons for non-participation. The following data will be collected during visit 1:

- ▶ 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.

### Box 1 Inclusion and exclusion criteria

#### Inclusion criteria

- ⇒ Aged ≥18 years.
- ⇒ Known history of diabetes.

#### 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).

**Table 1** Visit schedule

Visit no	Screening	Planned/routine visit	Blood test (in some centres)	Reference scan
	0	1	1b	2
Screening	X			
Study information material	X			
Informed consent		X		
Inclusion and 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)†	
Reference scan (CTA/MRA)				X

\*Repeat tests will only be performed in the first 100 volunteering patients.

†The blood test to assess renal function may require a separate, additional visit at some centres.

‡EQ-5D-5L, EuroQol- five-dimensional- five-level questionnaire

CTA, CT angiography; MRA, MR angiography.

- ▶ Foot examination: neuropathy, presence of DFU, DFU severity using the WiFi classification system.<sup>25</sup>
- ▶ 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.
- ▶ Patient quality-of-life: EQ-5D-5L (EuroQol- five-dimensional- five-level) questionnaire.

### Interventions: index tests

Primarily we will be evaluating five index tests (ABPI, exercise ABPI, TBPI, visual handheld Doppler and audible handheld Doppler). In four centres, we will evaluate the PAD-scan as a sixth test. We have chosen not to evaluate this test at all centres, as DUS machines are moderately costly and not currently available at every site. The sites chosen to perform the PAD-scan have DUS machines available in their clinics to perform this.

All tests performed in clinic (or on the ward if the participant is admitted to hospital), during visit 1, by a member of the local clinical team so that results are generalisable. Tests will be performed on one limb; the most problematic side in symptomatic patients or a randomly selected side in asymptomatic patients. Tests and equipment will be standardised and team members will undergo protocol training.

Ideally, test order would be randomised to minimise influence carrying over from one test to the other. However, the audible and visual waveform tests involve semiobjective interpretation and therefore could be influenced by knowledge of the tests with an objective output (TBPI, ABPI and exercise ABPI). Therefore,

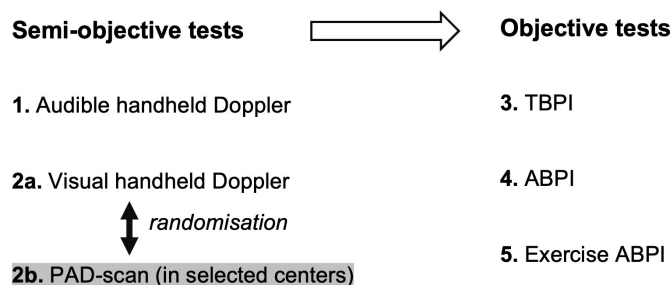
semiobjective waveform tests will be performed first followed by the fully objective tests. Randomising the order of tests in these two blocks is not possible:

- ▶ Semiobjective 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](#).

### Conducting index tests

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



**Figure 2** Order of index tests. ABPI, Ankle Brachial Pressure Index; PAD, peripheral arterial disease; TBPI, Toe Brachial Pressure Index.



of index tests and diagnostic threshold are provided in online supplemental appendix 2.

### 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 intrarater and inter-rater reliability, respectively. Tests will be performed using the same descriptions outlined above. A minimum of 10 min rest must be provided to the patient prior to each batch of tests to avoid influence from previous tests carrying forward.

### Reference test

Digital subtraction angiography (DSA) is considered the gold standard for the diagnosis of PAD. However, it is invasive and carries risks. Given the previously mentioned limitations of DUS our reference test will be cross sectional arterial imaging with CTA or MRA. Both have excellent accuracy compared with DSA.<sup>26 27</sup> Some of our centres use only CTA, whereas others use only MRA. Additionally, some patients in our Patient and Public Involvement (PPI) survey reported that they would not take part if CTA was mandated 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 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 online supplemental appendix 3. 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 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 rereported centrally by a blinded consultant radiologist at the core lab (hosted by the 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-rater and intrarater reliability in the core lab, 15% of scans will be rereported by our core lab radiologists.

Scans at the core laboratory will be assessed using a validated angiographic scoring system (ANGIO score; online supplemental appendix 4)<sup>28</sup>; 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  $\geq 50\%$ ; 2, complete occlusion). The presence of one or more arterial lesions of  $\geq 50\%$  stenosis will be used as threshold for the diagnosis of PAD. Tandem lesions with a combined value of  $\geq 50\%$  will also be considered positive for PAD as they are haemodynamically significant and in certain scenarios (eg, non-healing DFU) may prompt treatment. PAD severity will also be categorised according

to the ANGIO score, as mild ( $\leq 4$ ), moderate<sup>5–9</sup> or severe ( $\geq 10$ ). These categories have been shown to correlate with risk of amputation and cardiovascular events.<sup>28</sup>

### Outcomes

#### Primary outcome

Sensitivity of index tests.

#### Secondary outcomes

Specificity, likelihood ratios, predictive values and diagnostic OR.

- ▶ 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 and (3) ICER at 5 years.
- ▶ Patient acceptability (online supplemental appendix 5).
- ▶ Technical success.
- ▶ Inter-rater and intrarater 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.

### Statistical analysis and plan

#### Sample size

Assuming a PAD prevalence of 50% (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% CI 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 five 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,<sup>29</sup> the estimate to reflect the findings of our systematic review has been adjusted; the prevalence of 50% across 18 studies.<sup>11</sup> 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.

#### Sample size calculations for inter-rater 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 lost 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 (eg, 0.22 positive–negative vs 0.05 negative–positive).

### Internal pilot

A stop-go assessment of recruitment feasibility will be included after a 4-month internal pilot. Recruitment feasibility will be assessed at the end of month 4, when 136 participants should have been recruited. If 90 or fewer have been recruited, the study may be stopped (RED); between 90 and 114 adapt (AMBER—more sites and/or more time) and if 115 or more continue unchanged (GREEN—within sampling variability of our target). This will be discussed with the trial steering committee (TSC) and the funder.

### 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 ratios and diagnostic OR (using the bivariate model approach implemented in R). A 95% CIs 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 (ie, 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 delta adjustment approach given by van Buuren will be followed<sup>30</sup> and also the recommendations of Molenburghs and Kenward.<sup>31</sup> 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 (SAP) will be prespecified. Any further subgroup analysis (eg, if suggested later by new data external to the study) will be labelled as exploratory. Prespecified 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. Both will be analysed as prespecified subgroup analyses in the SAP.

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 prespecified in the SAP and then, acknowledging the paired data, use the approach of Pepe and Thomson,<sup>32</sup>

which looks at linear combinations of the underlying tests. Post hoc checks will be made if there were combinations that were not prespecified that performed even better, as hypotheses for subsequent evaluation.

It is important to quantify the ability of each of the five 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 intrarater repeatability (or reproducibility) will be undertaken using the test–retest approach.<sup>33 34</sup> The inter-rater reliability (the agreement between two or more clinicians measuring the same subject, again as under the conditions above) using appropriate methodology<sup>33 34</sup> will be quantified. For the inter-rater and intrarater repeatability, we will aim for a sample size of 100 per a 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 intrarater repeatability, or unacceptable inter-rater reliability, it could be dropped from further consideration, following discussions with the independent TSC. Unacceptable intrarater 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,<sup>35</sup> with a kappa of <0.4 considered unacceptable. There is no 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-rater and intrarater 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 SAP, authored by the study statistician and agreed by the independent TSC. The SAP will be prepared and finalised prior to database lock.

### Health economics analysis

The health economic analysis aims to assess the likely impact of a more accurate diagnostic test on treatment choices, health outcomes that are important to patients (namely DFU incidence and healing time, cardiovascular events, amputations and mortality), and the impact on use of national healthcare system resources of testing, preventative interventions and treatments of disease. As there will not be clinical follow-up in the DM PAD study to determine these outcomes, these questions will be addressed by modelling methods that simulate clinical events that would occur in these patients under different counterfactual testing options. A literature review will be conducted to identify published health economic studies in similar patient groups. The structure and evidence that will be used in constructing the model will be determined following this review but may follow and update previous

work by this group.<sup>14</sup> Depending on ulceration status at presentation, this model classified patients 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). It was assumed that true and false positive patients without DFU would be prescribed orthotics and additional foot checks, in addition to standard care. True and false positive patients with DFU would undergo confirmatory imaging and, if confirmed positive, angiography, revascularisation and low-dose rivaroxaban, in addition to standard care. True and false negative patients would continue with standard care for the remainder of the 5-year time horizon. 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 (eg, orthotics, revascularisation, rivaroxaban) were obtained from national evidence reviews and the literature.

The study will be conducted from the perspective of the UK NHS and Personal Social Services according to established methodological guidelines and reporting standards.<sup>36</sup> Prices and unit costs of healthcare resources will be obtained from manufacturers and national databases.

### Data management

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

Data management will be through REDCap, a web-based data entry system and database. The data management services team (based at Edinburgh Clinical Trials Unit) will work with the investigators, trial Manager, trial statisticians and trial teams to design and build bespoke electronic CRFs and validation rules for data entry to ensure that the data are 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.

### Study management

The organisational structure for the study, including details of monitoring procedures, quality control and assurance, is outlined in online supplemental appendix 6.

### Patient and public involvement

The development of the proposal has been informed by patients and the public.

### Learning from the experience of patients in the TrEAD study

A telephone survey of 57 patients from the TrEAD study followed by a focus group discussion 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. 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 general practitioner 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, where feasible, at the same location as index tests.

### 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’.

### Ongoing PPI

Our patient coinvestigator, EP will chair a patient advisor group who will meet annually to ensure that a wide range of patient perspectives are considered during the study. The patient advisor group will also contribute to the interpretation of study findings, thereby allowing us to integrate patients’ perspectives in the analysis phase.

## ETHICS AND DISSEMINATION

### Ethics

The study has received approval from the National Research Ethics Service (NRES) London Central Committee (Reference 21/PR/1221). The study has been registered on ClinicalTrials.gov (Registration number NCT05009602).

### Dissemination plan

Results will be reported according to the Standards for Reporting of Diagnostic Accuracy Studies checklist.<sup>37</sup> Results will be disseminated through scientific conferences and peer-reviewed publications. Study participants and relevant patient support groups will be informed of the study results.



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## SUPPLEMENTARY MATERIAL

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## Appendix 1- Patient information sheet and informed consent document

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A multicenter comparative diagnostic accuracy study

### Diagnostic tools to establish the presence and severity of peripheral arterial disease in people with diabetes (DM PAD)

**ISRCTN: 12358788**

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#### **Disclaimer**

*The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NHS, NIHR or the Department of Health.*



## PATIENT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT

*You have been invited to take part in a research study called DM PAD. Before you decide whether to accept, we would like to explain why the research is being carried out and what it will involve.*

*Please read this information carefully, and discuss it with others if you wish. Ask us if anything is unclear, or if you would like more information.*

- *Part 1 tells you the purpose of this study and what will happen to you if you take part.*
- *Part 2 gives you more detailed information about the conduct of the study.*

*Please take your time to decide whether or not you wish to take part.*

**Thank you for reading this information sheet.**

## **Part 1**

### **What is the purpose of the study?**

In the UK there are over 7,000 leg amputations each year because of diabetes. The most important cause of this is poor circulation. The detection of poor circulation in patients with diabetes is difficult. A number of tests exist to detect poor circulation (known as peripheral arterial disease). However, there is confusion as to which is the gold standard. We propose to carry out this study to determine which test is the most accurate.

### **Why have I been chosen?**

You have been invited to consider this study because you are a patient with diabetes. We hope that about 730 people like you from across the UK will take part in this study.

### **Do I have to take part?**

No, participation in this study is entirely voluntary. If you do decide to take part you will be given this information sheet to keep. You will be asked to sign a consent form, but you are still free to withdraw at any time and without giving a reason. If you decide not to take part in the study, your doctor will be happy to talk through how he/she will treat you outside of the study. You do not have to give a reason for not taking part and your treatment and care will not be affected in any way.

### **What will happen to me if I take part?**

If you choose to be involved in the research, your participation will last 6 weeks from trial entry. Although the study is conducted over 2 visits, in most cases, the first visit will be conducted at the time of a routine visit that you already have scheduled. Therefore, you will only be required to make one additional visit. In some centres, an additional visit may be required to take a blood sample prior to the imaging scan (i.e. 3 visits in total). Your doctor or nurse will inform you if this is the case. We have designed the study in this way to make it as easy as possible for you to take part.

If you are currently an inpatient, your first visit will be conducted at your bedside. Where possible, if you remain an inpatient, your second visit scan will also be performed during your inpatient stay to avoid additional hospital visits.

The following section tells you more about what will happen on each of your visits.

There are no restrictions on your activity when you are taking part in this study. You will continue with any other medical care or treatments, such as taking regular medication, as you would normally do. This will include the standard treatment for diabetes, which may include dietary advice, blood glucose management and drug treatment.

### **Your first visit**

If you decide to participate in the study your first visit will coincide with a routine visit that you will have booked as part of your standard care, irrespective of whether you wish to participate in the DM PAD study. The following steps will be taken at your first visit, which will last approximately 1 hour 10 minutes (i.e., 40 minutes longer than your routine scheduled appointment):

- You will first be asked to sign the consent form to confirm that you would like to be included (you will be given a copy of this).
- Some information about your medical history and current medical condition will be collected to check that you are able to take part.

If the research team confirm that you are able to take part in the study, you will have your blood pressure and pulse rate measured. Other measurements that will be recorded include height, weight and body mass index. We will also ask some questions regarding demographic details, including your gender and ethnicity.

At this visit you will also be asked to complete a health questionnaire about your quality of life so we can collect information about your health. This is called the EQ-5D-5L questionnaire.

As part of your routine care, a doctor or nurse will perform an assessment for neuropathy and, if relevant, assess the severity of your foot ulcer. A blood test to assess your renal (kidney)



function will also be taken in preparation for visit 2. This blood test may require a separate, additional, visit at a different site. Your doctor or nurse will inform you if this is the case.

A total of five different tests will be performed on either one (visible and audible blood flow) or both (blood pressure measurements) legs. A number of these tests are routinely performed, others, marked with an asterisk (\*) are additional tests that are being evaluated in this study:

1. Blood pressure measurements at the arm and ankle;
2. Blood pressure measurements at the arm and ankle following repetitive heel raises\*;
3. Blood pressure measurements at the big toe\*;
4. Visible blood flow waveform (using a handheld Doppler)\*;
5. Audible blood flow waveform (using a handheld Doppler);

The visible and audible waveform assessments involve a handheld Doppler device to check for the presence or absence of a signal in the arteries in the leg. The visual blood flow waveforms will be saved using a code that means you cannot be directly identified ('pseudonymised'), and may be used for future analysis"

For each of the tests, you will be asked to rate your experience.

In certain centres, a sixth test will be performed, called a Podiatry Ankle Duplex scan (PAD-scan)\* on one leg. This is a new ultrasound test that directly visualises the ankle vessels and detects more detailed waveforms.

The visible and audible handheld Doppler tests, as well as the PAD-scan, are very similar. They all involve the brief application of a sensor and gel on the skin to assess the quality of blood flow to the foot.

A sub-group of 100 patients will be asked to consent to having all the above index tests repeated (in the same leg) on the same day, by the same operator and also by an alternative operator to assess reliability. This will take an additional 40 minutes.

### **Your second visit**

The second visit will take place within 6 weeks of the first visit and may take place at a different participating site if you were recruited into the study at a primary care site or in the community (due to access to imaging equipment). Your doctor or nurse will inform you if this is the case. In the second visit, which will take 30 minutes, you will have a more detailed scan of your blood vessels in your leg using a computed tomography angiography (CTA) or magnetic resonance angiography (MRA) scan. If you were to choose not to take part in this study there would still be a 2 out of 10 (20%) chance that you would still undergo one of these tests for further evaluation. The results from the index tests will be compared to the results of the CTA or MRA to identify the most accurate test.

Your doctor or nurse will inform you of which scan (CTA or MRA) will be performed prior to your appointment. In some centres, both scans may not be available as an option.

If you are on metformin, you may be advised to withhold this before the scan for a short period of time.

### CTA

CTA uses x-rays with detectors and a powerful computer to produce two-dimensional and three-dimensional images of the blood vessels.

An injection of a contrast dye will be given into a vein in the arm to highlight blood vessels. You will lie on your back in the scanner. You must hold your breath and remain still while the scans are taken. The contrast dye injection gives a sensation of warmth, and sometimes a metallic taste in the mouth which is normal – this rapidly clears.

The images are then processed by a powerful computer which can then display the arteries clear of the soft tissues around them to give an accurate diagnosis of any disease of the arteries.

The scan will last approximately 5-10 minutes in total.

CTA is associated with some radiation exposure. More information on this is provided later in this information sheet.

### MRA

MRA is a type of MRI scan which uses powerful magnets, radio waves and computers to generate images of the body, specifically to look at the blood vessels. To get best views, it is usually necessary to give some contrast medium into your vein at the time of the scan. The scanner is a large tube which you lay inside on a scan table. The table moves through the scanner to take images of your body. You will need to lie as still as possible. During the scan you will hear loud knocking noises, which occur in bursts during each imaging sequence.

The scan usually takes about 15 - 20 minutes.

MRA scans may not be recommended in certain situations. For example, if you have a metal implant fitted such as a pacemaker, internal cardiac defibrillator, cochlear implants in your ear, a nerve stimulator, surgical clips or any implants).

### **What is the standard treatment in the UK?**

If you decide not to take part in the trial, in most hospitals you will be offered the standard care for diabetes which includes dietary advice, blood glucose management and drug treatment.

### **Unwanted effects of treatment**

You should not join the study if you are pregnant (or plan on becoming pregnant during the course of the study), have renal impairment, have a known hypersensitivity/allergy to contrast medium, or have non-compatible implants (for patients undergoing an MRA only).



## Pregnancy

CTA and MRA scans are contraindicated in pregnant patients. Pregnant women must not therefore take part in this study; neither should women who plan to become pregnant during the study. Women who could become pregnant will be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy and must use an effective contraceptive during the course of this study. Contraceptive methods that can achieve a failure rate of less than 1% per year and when used consistently and correctly are considered as highly effective birth control methods. These include:

- ✓ combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- ✓ progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- ✓ intrauterine device (IUD)
- ✓ intrauterine hormone-releasing system (IUS)
- ✓ bilateral tubal occlusion
- ✓ vasectomised partner
- ✓ sexual abstinence- if this is a compatible lifestyle choice

Any woman who finds that she has become pregnant while taking part in the study should immediately tell her research doctor. The research team may request to collect additional follow up information in such circumstances.

You may be withdrawn from the study if the doctor feels it is best for you not to participate or if you do not comply with the requirements of the study. If during the health screening tests any abnormal results are found, you will be immediately referred for clinical review as appropriate. If you feel any discomfort or distress during the study you must say so immediately and we will stop straight away. If for any reason during the study and you do not

wish to continue, than we will stop the tests immediately.

#### How is my condition monitored?

Participating in this study will not significantly affect how your condition is monitored or any other treatment you receive.

#### What are the possible benefits of taking part?

If you decide to participate, you will undergo comprehensive testing and imaging for peripheral arterial disease (poor circulation) as part of this study. If previously undiagnosed, the diagnosis of peripheral arterial disease may prompt your doctor to initiate medicines that will help reduce your chance of having a stroke, heart attack and worsening of your peripheral arterial disease.

Additionally, if you are diagnosed as having peripheral arterial disease, you may be eligible for additional measures to reduce the risk of developing a foot ulcer. These additional measures may include more frequent foot checks or new footwear.

If you have an active ulcer, a diagnosis of peripheral arterial disease will trigger a specialist review by a vascular surgeon for consideration of timely revascularisation to improve the chance of ulcer healing and reduce the risk of amputation.

You will not get paid for participating in this study but can claim for travel expenses.

#### What are the possible disadvantages and risks of taking part?

If you take part in this study you may have a Computed Tomography Angiography (CTA) procedure, which, for the majority of participants (about 80%), will be additional to the procedures you would have if you did not take part. This procedure uses ionising radiation to form images of your body and provide your doctor with other clinical information. Ionising radiation may cause cancer many years or decades after the exposure.

We are all at risk of developing cancer during our lifetime. 50% of the population is likely to develop one of the many forms of cancer at some stage during our lifetime. Taking part in this study may increase the chances of this happening to you to about 0.12% or 1 in 800.

CTA should NOT be used by the following individuals:

- pregnant women
- patients with renal impairment
- patients with a known hypersensitivity/allergy to contrast medium
- patients fitted with non-compatible implants (for patients undergoing an MRA only).

#### **What happens when the research study stops?**

The information from this study will be used to decide the most accurate test for the diagnosis of peripheral arterial disease in diabetic patients.

At the end of the trial you will revert to standard care for your condition.

#### **Will my taking part be kept confidential?**

Yes, it will. If you decide to participate, the information collected about you will be handled strictly in accordance with the consent form that you have signed and also the 2018 Data Protection Act. Please refer to Part 2 for further details.

**This completes Part 1 of the Information Sheet. If the Information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.**

#### **Part 2**

**What if relevant new information becomes available?**

Sometimes during the course of a research project, new information becomes available about a treatment that is being studied. If this happens, your research doctor will tell you about it and will discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

### **What will happen if I don't want to carry on with the study?**

You can decide to leave the study at any time. You do not need to give a reason.

If you leave the study before your treatment, then your doctor will discuss with you what type of treatment they will use outside the study. If you decide to leave the study, any data collected up until that time will remain on file and will be included in the final study analysis and follow up information will continue to be collected from your medical records.

If you decide to leave the study and do not wish for any further data to be collected about you, you should inform your clinical care team of this in order that no further follow up information is collected from your medical records. In line with Good Clinical Practice guidelines, at the end of the study, your data will be securely archived. In this study, data will be archived for a minimum of 10 years after which arrangements for confidential destruction will be made.

### **What if something goes wrong?**

A group of independent researchers (called the Data Monitoring Committee) will closely monitor the study. If there are any problems then they will be detected as soon as possible so that the study can be changed or stopped if necessary.

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of

the way you have been treated during the course of this study then you should immediately inform the Investigator ([Insert name and contact details](#)). The normal National Health Service complaints mechanisms are also available to you. If you are not satisfied with the response, you may contact your local Patient Advice and Liaison Service (PALS) which offers confidential advice, support and information on health-related matters ([insert contact details](#)). You may also contact the Imperial AHSC Research Governance and Integrity office (Room 215, Medical School Building, St. Marys Campus, Norfolk Place, London W2 1PG. Tel: 0207 594 9459).

### **How will we use information about you?**

Imperial College London is the sponsor for this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Imperial College London will keep your personal data for:

- 10 years after the study has finished in relation to data subject consent forms.
- 10 years after the study has completed in relation to primary research data.

We will need to use information from you, your medical records and possibly your GP for this research project.

This information will include your initials, NHS number, name and contact details such as telephone number and address. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Some of your information will be sent to the University of Granada based in Spain, and the University Hospitals of Leicester NHS Trust based in the United Kingdom. They must follow our rules about keeping your information safe.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

**Legal basis**

As a university we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the [UK Policy Framework for Health and Social Care Research](#)

**International transfers**

There may be a requirement to transfer information to countries outside the European Economic Area (for example, to a research partner). Where this information contains your personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a European Commission (EC) adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient organisation that incorporates EC approved standard contractual clauses that safeguard how your personal data is processed.

**Sharing your information with others**

For the purposes referred to in this privacy notice and relying on the bases for processing as set out above, we will share your personal data with certain third parties.

- Other College employees, agents, contractors and service providers (for example, suppliers of printing and mailing services, email communication services or web services, or suppliers who help us carry out any of the activities described above). Our third party service providers are required to enter into data processing agreements with us. We only permit them to process your personal data for specified purposes and in accordance with our policies.
- the following Research Collaborators / Partners in the study;



- University of Granada - the Health Economist is based at the University of Granada and therefore your de-identified health economic and quality of life data will be transferred there.
- University Hospitals of Leicester NHS Trust - the scan you have performed at your second visit (CTA or MRA) will be reported by a radiologist at University Hospitals of Leicester NHS Trust and therefore your medical scan images will be transferred there via a secure NHS system.
- University of Edinburgh - with your permission, your data will be entered onto a secure database held at the University of Edinburgh, in accordance with the 2018 Data Protection Act.

**What are your choices about how your information is used?**

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

Anonymous data may also be linked with appropriate national 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.

**Where can you find out more about how your information is used?**

You can find out more about how we use your information

- at [www.hra.nhs.uk/information-about-patients/](http://www.hra.nhs.uk/information-about-patients/)
- by asking one of the research team
- by sending an email to DM-PAD@imperial.ac.uk, or
- by ringing us on 0203 311 5208.

**Complaint**

If you wish to raise a complaint on how we have handled your personal data, please contact Imperial College London's Data Protection Officer via email at [dpo@imperial.ac.uk](mailto:dpo@imperial.ac.uk), via telephone on 020 7594 3502 and/or via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ.

If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO). The ICO does recommend that you seek to resolve matters with the data controller (us) first before involving the regulator.

**Involvement of the General Practitioner (GP) / Family Doctor:**

With your permission, your GP and other doctors involved in your clinical care will be kept informed of your participation in the study, but otherwise all information about you and your treatment will remain confidential. We may contact your GP to obtain information about your health status if we cannot reach you.

**What will happen if I lose mental capacity during the study period?**

This is expected to be a very rare occurrence. If this did occur your doctor or carer will determine whether you should be withdrawn from the study. If you are 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 you.

**What will happen to the results of the research study?**

When the study is complete, we plan to inform patients of the results of the study by letter, email, newsletter, social media or publication on the trial website. We may ask patients if there are any other methods they would prefer. The results will be presented at conferences and published in a medical journal. No individual participants will be identified.

**Who has organised, reviewed and funded the research and who will be supervising it?**

This research has been supported by a National Institute for Health Research, Health Technology Assessment programme grant, which is funded by the National Institute for Health Research. The Sponsor of this study (Imperial College London) will pay your hospital to cover the costs of your participation in this study. You are able to claim the travel costs (e.g. bus / train / tube fare or parking costs and petrol) for your hospital visits. Please speak to the study nurse about how to make this claim.

The research is being co-ordinated by Imperial College London, who have overall responsibility for coordination of the study. The research has been reviewed by the National Institute for Health Research, representatives from all of the participating hospitals and organisations, and an independent National Research Ethics Committee, and the Health Research Authority (HRA).

**Contact Details**

If you have any further questions about your treatment, please discuss them with your doctor.

You may also find it helpful to contact the research nurse on XXXXXX.

If you would like further information about clinical research, the UK Clinical Research Collaboration (a partnership of organisations working together on clinical research in the UK) has published a booklet entitled 'Understanding Clinical Trials'. Contact UKCRC: website: [http://www.ukcrc.org/wp-content/uploads/2014/03/iCT\\_leaflet.pdf](http://www.ukcrc.org/wp-content/uploads/2014/03/iCT_leaflet.pdf)

**THANK YOU FOR READING THIS INFORMATION SHEET**



**Delete this line, then print on Hospital/Trust headed paper**

Site ID:	Initials:
Participant Trial ID:	Principal Investigator Name:

**Diagnostic tools to establish the presence and severity of peripheral arterial disease in people with diabetes (DM PAD)**

**IRAS 301408**

**PATIENT CONSENT FORM**

Please initial box

1. I confirm that I have read and understand the information sheet dated 06/10/2021 (Version 2.0) for the above study and have had the opportunity to ask questions which have been answered fully.
2. I understand that my participation is voluntary and that I am free to leave the study at any time without my medical care or legal rights being affected.
3. I understand that relevant sections of my medical records may be looked at by authorised individuals from the research team, from regulatory bodies, from the study Sponsor, or from the NHS Trust in order to check that the study is being carried out correctly. I give permission, provided that strict confidentiality is maintained, for these bodies to have access to my medical records for the above study.
4. I agree to my data being entered onto a secure database held at the University of Edinburgh, in accordance with the Data Protection Act 2018.
5. I understand that my pseudonymised data will be transferred to the University of Granada for the analysis.
6. I understand that my CTA or MRA scan images will be transferred to the University Hospitals of Leicester NHS Trust for reporting.
7. I agree to my GP, or any other doctor treating me, being notified of my participation in this study. I agree to my GP being involved in the study, including any necessary exchange of information about me between my GP and the research team.

8. If during the study my clinical care team determine that I have lost capacity to provide informed consent, I will be withdrawn from the study and any identifiable data collected with consent would be retained and used in the study.

9. I agree to take part in the DM PAD study.

**Optional consent section (please initial the appropriate box)**

10. I give/do not give consent for information collected about me to be used to support other research in the future, including those outside of the EEA.

Give consent

Do not give consent

11. I give/do not give consent for my data may be linked with appropriate national 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

Give consent

Do not give consent

12. I give/do not give consent to be contacted in the future with regards to this study, should the study be extended.

Give consent

Do not give consent

\_\_\_\_\_  
Full Name of Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of Person Taking Consent

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

(1 copy for participant; 1 copy for the patient's medical notes, 1 copy for the site file)

## Appendix 2- Details of index tests

### Index tests

#### **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 (26,27) and has been advocated by the American Heart Association (28). Our PPI focus group considered this test acceptable.

The exercise ABPI protocol, will consist of 50 consecutive repetitions of active dorsiflexion whilst standing (26). 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. The highest brachial upper limb reading will be 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).

**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  $<60^\circ$ . Waveforms will be optimised for interpretation by adjusting sample volume, sample size, Doppler scale, Doppler gain and wall thump filter settings.

**Diagnostic thresholds**

We will evaluate the performance of the index tests based on prespecified diagnostic thresholds for PAD. 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, we will evaluate different 'exploratory' thresholds as part of our secondary analyses. For tests generating continuous results (ABPI, TBPI and exercise ABPI) we will also evaluate performance based on optimised thresholds derived from Receiver Operating Characteristics (ROC) analysis. We will use a 'net benefit' approach (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:**

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

## Appendix 3- Reference CTA and MRA protocol

### 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 mm<sup>2</sup> 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.

## Appendix 4- Angio score

(INSERT)

## Appendix 5- Evaluation of patient acceptability Likert scale

<b>Overall, how satisfied were you with each of the tests you have had today?</b>					
					
	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)					



## Appendix 6- 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.

### **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.

### **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.

### **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.

### **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.

### **Patient Advisory Group**

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

### **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.

### **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.

### **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.

**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.

**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.