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1. Title of the project

Automated ankle brachial pressure index measurement devices for assessing peripheral arterial disease in people with leg ulceration

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3. Plain English summary

Leg ulcers are long-lasting wounds that develop between the knee and the ankle and are slow to heal. They are common in adults, especially in older people. Most leg ulcers happen because of problems in the blood flow in the veins and usually are treated by applying bandages or stockings that squeeze the leg to create a 'compression' effect. However, this can harm the blood flow in the leg and should not be used in people with a condition called Peripheral Artery Disease, abbreviated as PAD. The main symptom is leg pain when walking. If untreated, PAD can cause serious problems including the risk of leg amputation. People with PAD are also at risk of developing heart problems and stroke. It is important to make sure that people with leg ulcers receive the right treatment and therefore it is recommended to check whether they suffer from PAD. To recognise the presence of PAD and identify people who should not receive compression therapy, the medical staff use a measurement called 'Ankle Brachial Pressure Index' or 'ABPI', which measures the pressure in the ankle. ABPI measurement is usually carried out by medical staff using a hand-held device (called Doppler ultrasound) and a manually inflated blood pressure cuff. The procedure is time-consuming and usually, people with leg ulcers find it uncomfortable. Automatic devices can be used instead of hand-held devices to speed up the procedure and make it more acceptable for people with leg ulcers. However, we need to know whether these devices produce reliable results and offer additional benefits compared to current methods (for example if they are easier or faster to perform and more comfortable for the person being tested).

The purpose of this assessment is to bring together the data available and decide whether the use of automated devices for identifying PAD in people with leg ulcers is effective and represents good value for money as well as good use of NHS resources. We intend to compare the costs (e.g., cost of the device, cost of treatment) and benefits (e.g., patient survival and quality of life) of the existing automated devices to determine the best use of NHS resources and inform clinical practice and policy.

4. Decision problem

4.1 Purpose of the decision to be made

Peripheral artery disease (PAD) involves narrowing of the peripheral arteries resulting in restriction of blood supply to the affected limb and is most commonly caused by atherosclerosis.[1, 2] PAD is caused by narrowing or blockage of the arteries by fatty deposits known as atheroma, leading to restrictions in blood flow to the body part supplied by the pertinent artery.[3, 4] The most common symptom of PAD is pain on walking that is relieved by rest (known as intermittent claudication; IC), but most people with PAD are asymptomatic.[1, 5, 6] Up to around one-quarter of those with symptomatic PAD will require intervention and a small number will progress to critical limb ischaemia, involving ulceration, gangrene and/or rest pain. If left untreated, amputation of the limb may be necessary.[1, 7, 8] Global prevalence of PAD of 10-15% has been estimated[7, 9, 10] and increases with age, especially in those aged in their 60s and 70s.[1, 2, 6] PAD is a risk factor for cardiovascular disease and stroke, is associated with morbidity or mortality from other atherosclerotic diseases (albeit unlikely to be the cause) and has prognostic value for underlying cardiovascular disease.[5, 6] Early treatment, therefore, reduces mortality.[4] NICE guideline CG147 recommends that people are assessed for the presence of PAD if they:

- have symptoms suggestive of peripheral arterial disease or
- have diabetes, non-healing wounds on the legs or feet or unexplained leg pain or
- are being considered for interventions to the leg or foot or
- need to use compression hosiery.[11]

Measurement of ABPI is described in Section 4.4 below.

Leg ulcers are slow-healing wounds on the leg below the knee and on, or above, the ankle bone. It has been reported that around one million (or 2%) of adults in the UK have leg ulcers.[12] Most leg ulcers are caused by blood accumulating in the legs due to problems in the veins, namely venous ulcers.[13, 14] About 10% of leg ulcers are caused by peripheral arterial disease and in about 20% of leg ulcers, the underlying cause is both venous and arterial disease.[15-18] Compression treatment (bandages or stockings) has historically been used to treat venous leg ulcers and there is a large evidence base to support its effectiveness.[14] However, using compression to treat these ulcers may cause damage by impairing the arterial supply to the ulcerated leg. As this treatment is unsuitable for people with PAD,[13, 19] it is

recommended that people with leg ulcers are screened for arterial disease using the ankle brachial pressure index (ABPI).[13, 14] ABPI is measured using a sphygmomanometer and hand-held Doppler device, which requires expertise from the relevant operator/healthcare professional. The procedure can be a protracted and unpleasant for those with leg ulcers.[11, 13] Automated devices may be advantageous in reducing the length of time taken to assess ABPI and, thereby, any associated discomfort for the patient. In addition, automated devices may potentially be more accurate than manual processes in detecting PAD, thus conferring benefits such as reduced time to treatment and improved outcomes for people with leg ulcers.[20]

The purpose of this assessment is to review the current evidence on the performance and cost-effectiveness of devices for automated assessment of ABPI to help diagnose PAD in people with leg ulceration. The decision question as specified in the NICE final scope is "*are devices for automated assessment of ankle brachial pressure index (ABPI) a clinically and cost-effective alternative to a manual doppler test for assessing ABPI and peripheral arterial disease in people with leg ulcers*?"

4.2 Clear definition of the intervention

The technologies considered for this appraisal are devices that measure and calculate ABPI automatically, which are available to the NHS in England and have appropriate regulatory approval.

These technologies include doppler, oscillometry and plethysmography-based devices. Doppler-based devices use a doppler probe and provide doppler waveforms signals as an output while oscillometry-based devices assess oscillations in the vessel wall and plethysmography-based devices assess blood volume changes. The signal measured by these methods is either directly used to estimate blood pressure or assist the measurement of this with a pressure cuff. Devices that do not provide doppler waveforms signals may provide information about the quality of arterial circulation in the ankles instead. However, it is unclear whether these alternative outputs can be considered equivalent to doppler waveform signals. Current technologies comprise the BlueDop Doppler device (BlueDop Medical); the boso ABI-system 100 (BOSCH + SOHN), WatchBP Office ABI (Microlife) and WatchBP Office Vascular (Microlife) oscillometry-based devices; the MESI ABPI MD (MESI) and MESI mTABLET ABI (MESI) oscillometry and plethysmography-based devices; and the

Dopplex Ability Automatic ABI System (Huntleigh Healthcare), which is a plethysmography-based device. Table 1 illustrates the characteristics and features of these devices.

4.3 Population and relevant subgroups

The population under consideration is people with leg ulcers who need assessment of ABPI. Where data permits, the following subgroups may be considered:

- People with leg ulcers who need assessment of ABPI as part of their initial assessment.
- People with leg ulcers or healed leg ulcers who need re-assessment of ABPI as part of monitoring.
- People with diabetes, rheumatoid arthritis, systemic vasculitis, atherosclerotic disease advanced chronic renal failure or other conditions in which arterial calcification is common.
- People who have had lymph nodes removed or damaged, limb amputation or other conditions where blood pressure cannot be measured on both arms and legs.
- People with sickle cell disease.

Table 1 Summary of the characteristics of the devices considered for this appraisal

Test name	BlueDop (BlueDop Medical)	boso ABI-system 100 (BOSCH +SOHN)	WatchBP Office ABI (Microlife)	WatchBP Office Vascular (Microlife)	MESI ABPI MD (MESI)	MESI mTABLET ABI (MESI)	Dopplex Ability Automatic ABI System (Huntleigh Healthcare)
Components	• Hand-held egg-shaped doppler ultrasound device and tablet computer with software	• 2 arm cuffs, 2 ankle cuffs • Control panel	• 2 cuffs • Blood pressure monitor • Can be used with PC	• 2 cuffs • Blood pressure monitor • Can be used with PC	• 3 cuffs • Control unit with results screen	• 4 wireless cuffs • Medical tablet computer • Can integrate with electronic health records	• 4 dual-chamber cuffs • Control unit with results screen • Options for integrated printer and USB cable
How is the test done?	• Blood pressure in arms taken with a conventional blood pressure cuff • Ankle pressure measurements taken without cuff • ABPI calculated automatically as ratio between mean ankle and arm blood pressure	• Cuffs attached to upper arms and lower legs • Simultaneous oscillometric measurement on all 4 limbs • ABPI calculated automatically	• Cuffs applied to arms and button pressed on monitor • Cuffs inflate and deflate automatically and simultaneously, sense oscillations in the artery wall, algorithm estimates systolic blood pressure • Cuff is left on the arm with the highest pressure, another cuff is	• Cuffs applied to arms and button pressed on monitor • Cuffs inflate and deflate automatically and simultaneously, sense oscillations in the artery wall, algorithm estimates systolic blood pressure • Cuff is left on the arm with the highest pressure, another cuff is	• Cuffs applied and button pressed on control unit • Cuffs inflate and deflate automatically and simultaneously sense change in artery volume (plethysmography) and oscillations in artery wall (oscillometry), algorithm estimates systolic blood pressure	• Same as MESI ABPI MD except blood pressure is first measured simultaneously in both arms and then both ankles together with re- measuring in the arm that had the highest pressure	• Cuffs applied and play button pressed on control unit • Cuffs automatically inflate and deflate and sense change in artery volume and estimates systolic blood pressure (pneumatic plethysmography) • ABPI automatically calculated

Test name	BlueDop (BlueDop Medical)	boso ABI-system 100 (BOSCH +SOHN)	WatchBP Office ABI (Microlife)	WatchBP Office Vascular (Microlife)	MESI ABPI MD (MESI)	MESI mTABLET ABI (MESI)	Dopplex Ability Automatic ABI System (Huntleigh Healthcare)
			applied to legs one at a time and blood pressure measured as before • ABPI calculated automatically	applied to legs one at a time and blood pressure measured as before • ABPI calculated automatically	• ABPI calculated automatically		
Outputs	• ABPI • Doppler waveforms • Perfusion pressure • Vascular reserve • Can indicate whether the Doppler waveform signal is monophasic or multiphasic	• ABPI • Blood pressure • Difference s in blood pressure • Pulse • Pulse pressure • Indications of possible cardiac arrythmia disorders	• ABPI • Inter-arm difference • Atrial fibrillation (NICE MTG13)	• ABPI • Pulse wave velocity • Inter-arm difference • Atrial fibrillation (NICE MTG13)	• ABPI • Pulse waveforms • Pulse volume waveform (graph)	• ABPI • Pulse waveforms • Pulse volume waveform (graph) • Oscillations	• ABPI • Pulse waveforms • Pulse volume waveform (graph)
Time needed	• 1 minute to measure ABPI	• 1 minute to measure ABPI	• 10 to 15 minutes for whole procedure	• 10 to 15 minutes for whole procedure	• 1 minute to measure ABPI	• 1 minute to measure ABPI	• 3 minutes to measure ABPI
Patient resting and position for the test	• No need to rest before test	• Need to lie quietly	• At least 5 minutes rest before test	• At least 5 minutes rest before test	• No need to rest before test	• At least 5 minutes rest before test	• No need to rest before test

Test name	BlueDop (BlueDop Medical)	boso ABI-system 100 (BOSCH +SOHN)	WatchBP Office ABI (Microlife)	WatchBP Office Vascular (Microlife)	MESI ABPI MD (MESI)	MESI mTABLET ABI (MESI)	Dopplex Ability Automatic ABI System (Huntleigh Healthcare)
	• Sitting or lying down	without talking	• Need to lie flat and still for test	• Need to lie flat and still for test	• Need to lie flat and still for test	• Need to lie flat and still for test	• Need to lie flat and still for test
Indications for use	• Unclear	• Suitable for people whose upper arm circumferences are between 22 cm and 48 cm and ankle circumferences are between 18 cm and 38 cm. • Should not be used in people with severe heart failure	• For adults and children aged 3 years or older. • Should not be used in people for whom the use of blood pressure cuffs is not suitable (for example in people with arm and leg stents).	• For adults and children aged 3 years or older. • Should not be used in people for whom the use of blood pressure cuffs is not suitable (for example in people with arm and leg stents).	• For people aged 10 years and over.	• For people aged 10 years and over.	• For people aged 18 years or older. • Should not be used in people with PAD (ankle systolic pressure<60m mHg) • Should not be used if the leg is affected by gangrene, recent skin graft, dermatitis, cellulitis, or untreated wounds. But it may be used on the unaffected leg. • Minimal training is needed to use the device.

4.4 Clinical pathway

Assessment and treatment of leg ulcers in the NHS is conducted according to the recommendations of the National Wound Care Strategy Programme (NWCSP).[13] Recommended immediate care for leg ulcers consists of cleansing and emollient, simple, low-adherent dressing with sufficient absorbency and mild graduated compression. People should be supported to self-care, if appropriate. If any of the following are present, immediate referral to the relevant clinical specialist is recommended: acute infection, symptoms of sepsis, acute or chronic limb threatening ischaemia, suspected deep vein thrombosis or suspected cancer. The NWSCP further recommends that assessment of leg wounds should take place within 14 days of original presentation.[13] The NWCSP[13] and the NICE Guideline CG147[11] both recommend including vascular assessment of arterial supply by way of ABPI. The guideline recommends measuring the ABPI by recording systolic blood pressure in both arms and in the posterior tibial, dorsalis pedis and, where possible, peroneal arteries. It is recommended that measurements are taken manually using a doppler probe of suitable frequency in preference to an automated system. The guideline also recommends documenting the nature of the doppler ultrasound signals in the foot arteries (pattern of the doppler waveforms). The type of waveform can provide information about the quality of arterial circulation and might identify issues even if a person has an ABPI that does not indicate arterial disease (e.g., people with arterial calcification). The index in each leg is calculated by dividing the highest ankle pressure by the highest arm pressure.

ABPI values are usually interpreted as follows:

- less than 0.8 suggest arterial disease
- less than 0.5 suggest severe arterial disease
- between 0.8 and 1.3 suggest no arterial disease and
- greater than 1.3 suggest arterial calcification.

Values above 1.5 indicate that the vessels are likely to be incompressible and the results are not reliable. Results may be misleadingly high in people with diabetes, rheumatoid arthritis, systemic vasculitis, atherosclerotic disease, and advanced chronic renal failure, and should be interpreted with caution. In addition, caution should be exercised in using compression therapy in people with diabetes due to potential arterial calcification and underlying sensory neuropathy.[21] The test can be uncomfortable for people with leg ulcers, due to both the need

to lie still during the test and the placement and inflation of the blood pressure cuff near an ulcer.

Treatment of **venous leg ulcers** with an adequate arterial supply should include strong compression therapy that is intended to apply at least 40mmHg compression, according to NWCSP recommendations.[13] The SIGN Guideline 120 for management of chronic venous leg ulcers also indicates that compression of at least 40mmHg should be applied [it is worth noting that the SIGN Guideline 120 was withdrawn in August 2020 and is currently under review].[22] Strong multi-component compression bandaging should be offered to people with chronic ankle/leg oedema not reduced by elevation, abnormal limb shape, copious exudate or very fragile skin. Cardiac clinicians should be consulted regarding the balance of the cardiac burden and using compression in people with advanced, unstable cardiac failure.

People with **leg ulcers with signs of arterial disease** should be referred for vascular surgical/endovenous interventions and advice on compression and NICE clinical guideline CG147 on diagnosis and management of peripheral arterial disease should be followed.[11] Whilst awaiting vascular expertise, mild graduated compression is appropriate in oedematous legs with no signs of arterial insufficiency.

People with **leg ulcers of other or uncertain aetiology** should be referred to a dermatologist and mild graduated compression used in the meantime if there are no signs of arterial insufficiency. For treating leg ulcers in people with lymphoedema, People with lymphoedema and ABPI <0.5 should not receive compression. Those with ABPI of 0.5-0.8 should receive reduced compression of 15-25mmHG. In addition, all should be referred to a vascular specialist.[23]

People with **mixed aetiology ulcers** have both venous disease and arterial disease and, without intervention, the arterial disease will take priority in decision making about treatments. There is currently no consensus on the appropriate level of compression for treating mixed leg ulcers and various criteria have been implemented.[24] The European Wound Management Association position document on compression therapy makes the following recommendations for treating people with mixed arterial and venous ulcers:[25]

- People with moderate arterial insufficiency with an ABPI 0.5-0.8: Reduced compression (15-25mg) if there is access to expert bandagers and teams with immediate access to vascular services; refer to vascular specialist particularly if continuing rest pain
- People with severe arterial insufficiency with an ABPI<0.5: Refer to vascular specialist. No compression. Many of these patients may benefit from either arterial surgery or interventional radiology.

Other recommendations for treatment of mixed ulcers include referral to tissue viability in the first instance. People with mixed aetiology ulcers will require close monitoring and reassessment of vascular status every three months, or sooner if the ulcer deteriorates.[26]

Ongoing care of leg ulcers should continue with a review of the effectiveness of the treatment plan at each dressing change. Documentation by way of wound photography at least every 4 weeks is recommended and escalation to the local specialist service if the ulcer does not show significant improvement or deteriorates. Additionally, at 12 weeks, the local specialist service should be consulted for the same reasons. Ulcers that have improved but not healed at this stage should be reassessed.

To **prevent recurrence of leg ulcers**, advice should be offered on skincare, footwear, exercise and mobility, rest and limb elevation, nutrition and self-care and, if appropriate, smoking cessation and weight loss. For people with healed venous leg ulcers, the NWCSP guidelines recommend the continuation of compression therapy and review every 6 months. Changes in symptoms or skin problems related to the compression hosiery should prompt a reassessment, including a vascular assessment of arterial supply.

The SIGN Guideline 120 for management of chronic venous leg ulcers indicated that compression of at least 40mmHg should be applied. The guideline was withdrawn in August 2020 and is currently under review.[22]

4.5 Key factors to be addressed

The research questions addressed by this assessment are the following:

1. Are devices for the automated assessment of ABPI (BlueDop doppler device [BlueDop Medical], boso ABI-system 100 [BOSCH + SOHN], Dopplex Ability Automatic ABI System [Huntleigh Healthcare], MESI ABPI MD [MESI], MESI mTABLET ABI (MESI), WatchBP Office ABI [Microlife] WatchBP Office Vascular [Microlife]) an effective alternative to the use of the manual Doppler test for assessing the presence of PAD in people with leg ulcers?
2. Does the use of these automated devices lead to improvements in clinical outcomes of people with leg ulcers?
3. Does the routine use of these automated devices affect costs to the NHS, length or quality of life (i.e., Quality Adjusted Life Years, QALYs), or cost-effectiveness measured as incremental cost per QALY gained for people with leg ulcers?

The main objectives of this assessment are the following:

- To determine the diagnostic performance and clinical utility of automated devices available in UK clinical practice (BlueDop doppler device [BlueDop Medical], boso ABI-system 100 [BOSCH + SOHN], WatchBP Office ABI [Microlife], WatchBP Office Vascular [Microlife]), MESI ABPI MD [MESI], MESI mTABLET ABI (MESI), Dopplex Ability Automatic ABI System [Huntleigh Healthcare]) for assessing the presence of PAD in people with leg ulcers.
- To develop an economic model to assess the cost-effectiveness of the automated devices available in UK clinical practice for assessing the presence of PAD in people with leg ulcers.

5. Evidence synthesis methods

This section describes the methods for addressing research questions 1 and 2 (diagnostic performance and clinical utility of the automated devices). Methods for addressing research question 3 (cost-effectiveness) are described in Section 6.

5.1 Inclusion and exclusion criteria

5.1.1 Population

People with leg ulcers who need assessment of ABPI.

5.1.2 Interventions

The interventions under investigation are the following devices for measuring ABPI:

- BlueDop (BlueDop Medical)
- boso ABI-system 100 (BOSCH + SOHN)
- WatchBP Office ABI (Microlife)
- WatchBP Office Vascular (Microlife)
- MESI mTABLET ABI (MESI)
- MESI ABPI MD (MESI)
- Dopplex Ability Automatic ABI System (Huntleigh Healthcare)

The current method for measuring ABPI as part of an initial clinical assessment for people with leg ulcers is a manual Doppler-based device: a hand-held doppler ultrasound probe and a manually inflated blood pressure cuff (sphygmomanometer). The doppler waveform output can identify health issues even if a person has an ABPI that does not indicate arterial disease. The procedure involves systolic pressure measurements on each limb and multiple measurements on the ankles. The doppler probe is placed on the artery to assess the blood flow in the artery. The sound of the blood flow stops when the cuff is inflated around the artery and starts again when the cuff is deflated. The systolic blood pressure is then assessed by the sphygmomanometer for calculating the ABPI.

People are required to lie down and remain still before and during the test. The procedure may take between 30 min to 1 hour to be completed according to the expertise of the operator and may involve two operators. The assessment is typically carried out by district or community nurses at a person's home, care home or a leg ulcer clinic, or by practice nurses at GP practices. The healthcare setting depends on the person's ability to attend the assessment outside of their home and local service arrangements. Scarcity in the required skills / training to conduct ABPI assessments may necessitate onward referral to specialist services after immediate care for the ulcer.

The NWCSP[13] recommends a full clinical assessment within 14 days of initial presentation but there is variation in current clinical practice.

5.1.3 Study design and Outcomes

The type of studies and relevant clinical outcomes considered suitable for inclusion are shown in Tables 2 and 3 below.

Table 2 Eligibility criteria for research question 1 (performance of devices for automated assessment of ABPI for detecting the presence of PAD in people with leg ulcers)

Population	**People with leg ulcers who need assessment of ABPI**
Devices under investigation	• BlueDop (BlueDop Medical) • boso ABI-system 100 (BOSCH + SOHN) • WatchBP Office ABI (Microlife) • WatchBP Office Vascular (Microlife) • MESI mTABLET ABI (MESI) • MESI ABPI MD (MESI) • Dopplex Ability Automatic ABI System (Huntleigh Healthcare)
Current method for measuring ABPI and detecting PAD	Manual Doppler device: a hand-held doppler ultrasound probe and a manually inflated blood pressure cuff.
Reference standard for detecting PAD	Imaging technologies including Duplex ultrasound, Angiography, Computed Tomography Angiography (CTA), Magnetic Resonance Angiography (MRA).
Outcomes	<u>Measures for consideration may include:</u> • Accuracy to detect peripheral arterial disease • Concordance between measurements by manual and automated devices • Concordance between measurements by different automated devices • Technical failure rate • Time required for using the device and calculating ABPI • Resources needed to do the test (for example, number of people or grade of staff needed to do the test) • Acceptability and experience of using the device
Study design	• Any cross-sectional study investigating the diagnostic performance of a single automated device as an alternative to a manual Doppler method for the measurement of ABPI and detection of PAD. • Any fully paired direct comparison in which one automated device is compared with either a manual Doppler method or another automated device in the same study population against an

	acceptable reference standard (e.g., Duplex ultrasound, Angiography, CTA, MRA). • Studies that assess the agreement between ABPI measurements obtained from an automated device with those obtained from a manual Doppler method or between 2 (or more) automated devices. • Studies of any design providing information on the use of the test (time to do test, technical failure rate, resources needed).
Healthcare setting	• Primary care (GP practice) • Community care (people's homes, care homes, community hospitals, leg ulcer clinic) • Secondary care

Table 3 Eligibility criteria for research question 2 (impact on clinical outcomes)

Population	**People with leg ulcers who need assessment of ABPI**
Devices under investigation	• BlueDop (BlueDop Medical) • boso ABI-system 100 (BOSCH + SOHN) • WatchBP Office ABI (Microlife) • WatchBP Office Vascular (Microlife) • MESI mTABLET ABI (MESI) • MESI ABPI MD (MESI) • Dopplex Ability Automatic ABI System (Huntleigh Healthcare)
Comparator	Measuring ABPI and assessing arterial circulation using a handheld doppler probe and manual blood pressure sphygmomanometer.
Outcomes	<u>Clinical outcomes for consideration may include</u>: • Morbidity (including any adverse events caused by assessment or treatment) • Mortality <u>Patient-reported outcomes for consideration may include:</u> • Health-related quality of life • Acceptability of using the device (including for example the position during the testing procedure) and patient experience.

	Intermediate measures for consideration may include: • Time to ulcer treatment • Time to ulcer healing • Number of referrals to specialist services (for example for ulcers that are not healing) • Number of hospitalisations • Number of leg amputations • Other healthcare resource use • Impact of test result on clinical decision-making • Rate of testing
Study design	• Randomised controlled trials • Single arm trials • Prospective and retrospective cohort studies
Healthcare setting	• Primary care (GP practice) • Community care (people's homes, care homes, community hospitals, leg ulcer clinic) • Secondary care

5.2 Search methods for identification of studies

5.2.1 Electronic searches

A sensitive literature search strategy will be developed by an Information Specialist to identify published peer-reviewed studies. Major electronic databases will be searched, including MEDLINE, Embase, Cochrane Library, Web of Science, and CINAHL. The search will focus initially on the approved devices listed in the NICE final scope; search facets defining the population of interest and health care location will be included if required to limit a large amount of literature. There will be no restrictions on date or language of publication at the time of the search. The reference lists of studies selected for full text appraisal will be screened for additional studies. Ongoing trials will be identified through searching major clinical trial registries. Websites of manufacturers, professional organisations, regulatory bodies and HTA organisations will be searched to identify additional relevant reports. Any additional information on potentially relevant studies provided by the manufacturers of the devices of interest will also be considered. All references will be exported to Endnote for recording and deduplication. A draft MEDLINE search is detailed in Appendix 1.

5.3 Study selection and data extraction strategies

One reviewer will screen the citations identified by the search strategies. A second reviewer will independently screen a random sample of citations (20%). Potentially relevant articles will be retrieved in full. Two reviewers will independently assess each article for eligibility based on the pre-specified inclusion criteria. We will resolve any disagreement by discussion or consultation with a third reviewer. Multiple publications of the same studies will be linked and considered together. For excluded studies, we will document reasons for exclusion. We will illustrate the study selection process by means of a PRISMA flow diagram.

Two reviewers will independently extract data from each eligible study using a customised form developed for the purpose of this assessment. Any disagreements will be resolved by discussion or consultation with a third reviewer.

The following information will be recorded from each study:

1. Characteristics of studies: first author, year of publication, country, language, setting, objectives, inclusion and exclusion criteria, type of enrolment.
2. Characteristics of study participants: age, sex, comorbidities, number of enrolled participants, numbers of limbs and participants included in the analysis, numbers and reasons for withdrawal.
3. Skills of the operator performing the measurement of ABPI using the devices under investigations or the reference devices (i.e., years of experience).
4. Characteristics of the automated devices under investigation (BlueDop [BlueDop Medical], boso ABI_system 100 (BOSCH + SOHN); WatchBP Office ABI [Microlife]; WatchBP Office Vascular [Microlife]; MESI ABPI MD [MESI]; MESI mTABLET ABI [MESI]; Dopplex Ability Automatic ABI System [Huntleigh Healthcare].
5. Characteristics of the reference standard device (i.e., manual Doppler method, Duplex ultrasound, angiography, CTA, MRA
6. The reported number of true positives, false positives, false negatives and true negatives and, when available, the area under the receiver-operating characteristic curve (AUC) for each device for each relevant outcome.
7. Measures assessing agreement between devices' measurements (correlation and reliability measures).

8. Relevant patient-reported, clinical and intermediate outcome measures, and information related to the use of the devices.

5.4 Quality assessment strategy

We will use QUADAS-2 criteria to assess the quality of included diagnostic studies.[27] QUADAS-2 consists of four domains: patient selection, index test, reference standard and flow and timing. Each domain is assessed in terms of 'low', 'high' or 'unclear' risk of bias, and the first three in terms of concerns regarding 'low', 'high' or 'unclear' applicability. We will use the QUADAS-C tool to assess the methodological quality of comparative diagnostic accuracy studies.[28]

We will use the Cochrane risk of bias tool[29] for the assessment of randomised trials evaluating the clinical utility of the automated devices under investigation (BlueDop [BlueDop Medical], boso ABI-system 100 [BOSCH + SOHN], WatchBP Office ABI [Microlife]; WatchBP Office Vascular [Microlife]; MESI ABPI MD [MES]; MESI mTABLET ABI [MESI]; Dopplex Ability Automatic ABI System [Huntleigh Healthcare]. For assessing the quality of non-randomised evidence reporting quantitative data on the clinical utility of the devices we will use the checklist developed by the HSRU, University of Aberdeen, in partnership with the NICE Review Body for Interventional Procedures (ReBIP). The ReBIP checklist was adapted from several sources[30-33] and comprises 17 items, which assess the following aspects: generalisability, sample definition and selection, description of the intervention, outcome assessment, adequacy of follow-up, and performance of the analysis.

One reviewer will extract the data and a second reviewer will check the data extracted. Any disagreements will be resolved by consensus or consultation with a third reviewer.

5.5 Methods of analysis/synthesis

Our primary analysis of interest will be the accuracy of each automated device under investigation as an alternative to the current manual Doppler method for assessing the presence of PAD in people with leg ulcers. We will use the methods recommended by Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy[34] and treat each device separately. For each device we will extract data (TP, FP, FN, and TN) to populate a 2x2 contingency table of test results cross-classified against those of an acceptable reference

standard. We will enter diagnostic data into Review Manager software (Review Manager 5.3), which will allow the sensitivity and specificity estimates together with their 95% confidence intervals (CIs) to be presented in forest plots and plotted in the receiver operating characteristic (ROC) space for each automated device.

Where appropriate we will perform meta-analysis of each pair of sensitivity and specificity estimates from each included study for each relevant device. To estimate a summary sensitivity and specificity point and corresponding 95% confidence region and 95% prediction region, we will use the bivariate logistic normal random effects model for meta-analyses with at least four studies.[35] In case of reported non-evaluable index test results we intend to analyse data according to the intention-to-diagnose principle.[36] We would classify participants with non-evaluable results as false positive if they had a negative reference standard, or false negative result if they had a positive reference standard. The meta-analyses will be performed using the NLMIXED procedure of the SAS software. We will perform separate meta-analyses for each device.

Heterogeneity will be assessed initially by visual inspection of the forest plots of sensitivity and specificity and of the prediction region in the summary ROC plots. If there are sufficient data, we will investigate sources of heterogeneity in estimates of test accuracy by adding covariates to the statistical model. We will assess the statistical significance of the covariate effect on sensitivity and specificity by using the log-likelihood ratio test for comparison of models with and without the covariate term. We will consider P values of less than 0.05 as statistically significant. We will consider the following potential sources of heterogeneity: characteristics of the population, type of reference standard (imaging methods for assessing the presence of PAD), healthcare setting (e.g., primary care, community care); operator skills assessed by years of experience.

If sufficient data are available, we will use sensitivity analyses to assess the impact of studies' methodological quality on the results of our analyses. We will restrict analysis to studies judged at low risk of bias.

We will not undertake a formal assessment of publication bias using funnel plot investigations as they are considered to produce seriously misleading results.[29]

When possible, we will also extract information on correlation and reliability measures (e.g., Pearson's correlation coefficient, intraclass correlation coefficient, Cohen's kappa coefficient) to assess the agreement between measurements by manual and automated devices or between measurements by different automated devices. This information will be tabulated and described narratively.

When appropriate, we intend to summarise the results of RCTs and observational studies evaluating the clinical impact of the use of automated devices in people with leg ulceration using standard meta-analysis methods.[29] We will consider a narrative synthesis of results if considerable clinical and methodological heterogeneity is observed between studies.

6. Report methods for synthesising evidence of cost-effectiveness

The specific objectives for the assessment of cost-effectiveness are the following:

- To review and critically appraise existing economic evaluations of devices for automated assessment of ABPI for diagnosing PAD in people with leg ulcers. Economic evaluations of the following devices will be included:
    - Doppler-based device: BlueDop (BlueDop Medical);
    - Oscillometry-based devices: boso ABI_system 100 (BOSCH + SOHN); WatchBP Office ABI (Microlife); WatchBP Office Vascular (Microlife);
    - Oscillometriy and plethysmography-based devices: MESI ABPI MD (MESI); MESI mTABLET ABI (MESI);
    - Plethysmography-based device: Dopplex Ability Automatic ABI System (Huntleigh Healthcare).
- To develop a *de novo* economic decision model to determine the cost-effectiveness of devices for the automated assessment of ABPI, compared with manual assessment as part of UK standard care for diagnosing peripheral arterial disease in people with leg ulceration from a UK NHS and personal social services perspective.

6.1 Identifying and systematically reviewing published cost-effectiveness studies

Comprehensive search strategies will be developed to identify economic evaluations of different approaches to measure ABPI. The following databases will be searched, with no date, language, or publication type restriction:

- Ovid MEDLINE
- Ovid EMBASE
- NHS Economic Evaluations Database
- HTA Database
- Research Papers in Economics
- ISPOR Scientific Presentations Database.

Websites of relevant professional organisations and health technology agencies (such as CADTH and others) will be consulted for additional reports. Reference lists of all included studies will be hand screened for additional studies.

Any identified full economic evaluations matching the NICE final scope will be included. Full economic evaluations are defined as comparative analyses of costs and outcomes in the framework of cost-utility, cost-effectiveness, cost-benefit, or cost-minimisation analyses. Economic evaluations conducted alongside single effectiveness studies (for example randomised controlled trials or cohort studies), or decision analysis models will be deemed eligible for inclusion. Included studies will be appraised against the NICE reference case for the assessment of the cost-effectiveness of diagnostic tests.[37] The main findings will be summarised in a narrative review, and results across studies will be tabulated for comparison. The suitability of identified full economic evaluations for answering the research questions outlined in the NICE final scope will be assessed and, if appropriate, study authors will be contacted to request access to model files that could be adapted or re-populated for this assessment.

6.2 Evaluation of costs and cost effectiveness

Following the review of cost-effectiveness evidence, if no suitable models to answer the research question can be identified, a *de novo* economic model will be developed to assess the cost-effectiveness of devices for the automated assessment of ABPI, compared with manual assessment for the diagnosis of peripheral arterial disease in people (adults, and where sufficient data allow, children) initially presenting with leg ulcers in primary care and

community care. The cost-effectiveness assessment will be developed and conducted in accordance with the NICE Diagnostics Assessment Programme manual recommendations.[37]

6.3 Development of a health economic model

6.3.1 Model structure

The specific details of the model type, pathway, and structure will be developed using an iterative process, first conducting a scoping search of existing economic models of the treatment and management of leg ulceration. Previous national and NICE guidance relevant to the decision problem will be consulted to ensure consistency with current recommendations where it is possible and appropriate to do so. An initial draft model structure will be validated for the context of this assessment with the EAG and the NICE specialist committee members for this topic. Where feasible, and where sufficient data exist as part of randomised controlled trials, the model will be built to consider the direct impact of automated versus manual ABPI measurement on health outcomes such as wound healing, amputation, and death. However, such data are unlikely to exist, in which case we will rely on a linked evidence approach to map the implications of diagnostic accuracy on appropriate / inappropriate referrals, treatment decisions and long-term health outcomes. We therefore anticipate a two-stage approach to modelling.

The first phase will be a decision tree model to incorporate diagnostic accuracy data from the diagnostic accuracy review and to allocate a cohort initially presenting with leg ulceration to PAD positive (true positive, false negative) and PAD negative (true negative and false positive) branches of the model, whereby a decision about referral to vascular / venous secondary care settings, and initiation of leg ulceration treatment will be made (this will involve a decision whether to use strong compression (recommended for venous ulcers) or not (not recommended for arterial ulcers). For the proportion who have mixed or arterial ulceration, the impact of the test result on decisions about the appropriate timing and strength of compression treatment, as well as appropriate referral and progression through the model pathway will be informed through further exploration of the clinical pathway with specialist committee members. The model will include available evidence regarding adverse health outcomes and costs associated delaying appropriate compression therapy (FP) and inappropriately applying compression therapy (FN).

National recommendations are that leg ulcers should be subject to a full clinical assessment within 14 days, though this rarely happens in clinical practice. The model base case analysis will assume that national recommendations are achievable for both automated and manual ABPI assessment, with scenario analyses exploring alternative hypothetical assumptions around the impact of potential reductions in delays achieving a full clinical assessment, if automated ABPI assessments could be implemented more widely, and more promptly, in primary care.

A Markov cohort state transition model, with several mutually exclusive health states will then describe the progression of leg ulceration over the longer term. Appropriate Markov health states may include healed ulcer, unhealed ulcer, amputation, and death. The model will incorporate the costs and outcomes of routine review of an ulcer's healing progress, according to the recommendations set out in the national wound care strategy for monitoring of healed ulcers, and the monitoring and escalation of care for unhealed ulcers.[13] Transition probabilities between the health states (expressed on a constant cycle length) will govern the flow of cohorts through the model, dependent on the accuracy of the initial test in determining whether the leg ulcer is vascular or arterial and whether initial compression treatment decisions have been appropriate or not.

6.3.2 Model parameterisation

The model will be populated using data obtained and synthesised from the systematic review of diagnostic accuracy and / or clinical outcomes studies as appropriate, as well as any relevant data obtained from the systematic review of cost-effectiveness studies. Additional targeted searches will be conducted, where appropriate, to inform population of key model parameters (e.g., resource use, probabilities, utilities). Priority will be given to data from systematic reviews (or updates of existing reviews) that are consistent with the NICE reference case.

Resource use and costs associated with the delivery of both automated and manual ABPI assessment will be based on a review of current clinical guidelines, published data, clinical expert opinion and data provided by manufacturers. Automated and manual ABPI assessment will be micro-costed and will include costs of staff time to deliver the test, to discuss results with senior colleagues, consumables and equipment and will be validated with clinical experts. The costs of any repeat-testing will be incorporated where necessary based on the

experience/opinions of the EAG's clinical experts and assessment subgroup experts. Unit costs for the alternative devices, and any associated consumables will be sourced from the companies (at the price most relevant to the NHS). Any required capital equipment costs will be selected based on standard UK practice and will be amortised over the estimated useful lifespan of the device and allocated on a per patient basis using estimates of annual throughput per device. The impact of varying annual through put for a device to account for use in different settings (e.g., home care setting by a district nurse) will be explored in scenario analyses. Resource use required in each health state will be based, wherever possible on national guidelines, validated in UK clinical practice by clinical experts. Scenario analyses exploring the impact of resource use following current, rather than recommended standard care, where these are different. UK national average unit costs will be used whenever possible, supplemented where necessary with study specific cost-estimates.

If feasible and if sufficient data exist, risks (probabilities) of the included events under standard practice will be informed by a review of published observational/registry data applicable to the UK clinical setting. Data from the control arms of identified randomised controlled trials will also be assessed for generalisability to the UK context. Health state utilities will be based on descriptive health related quality of life data elicited from UK patients using the EQ-5D and valued using UK general population preferences where possible.

Where appropriate evidence to populate key model parameters does not exist, assumptions based on clinical expert opinion may be required. Where clinical expert opinion is used to populate the model, uncertainty is greater, and so these assumptions will be tested in sensitivity analyses and a range of clinical expert views will be sought so that clinical expert opinion can be parameterised probabilistically within the model.

An NHS and PSS perspective will be adopted throughout, and the model will be run over a time period that is sufficient to realise all the costs and benefits of initial treatment decisions regarding treatment of leg ulceration. Costs and benefits (QALYs) that occur in the future will be discounted at an annual rate of 3.5% per annum.[37]

The results of the model will be presented in terms of a cost-utility analysis. A multi-test comparison will be undertaken, with each strategy compared incrementally to its next less

effective non-dominated comparator, to estimate its incremental cost per quality adjusted life year (QALY) gained. ICERs for pairwise comparisons of each automated test against current clinical management will also be reported. The modelling exercise will use the net benefit framework to identify the optimal testing strategy at different threshold ratios of willingness to pay per QALY. To characterise the uncertainty surrounding point estimates of incremental costs and effects, probabilistic sensitivity analyses will be undertaken. The results of these analyses will be presented in the form of cost-effectiveness acceptability curves (CEACs) and frontiers (CEAFs). Further deterministic sensitivity and scenario analyses will be used to address other forms of uncertainty. This will focus on areas where assumptions regarding the care pathway are required and for parameters where little or no high-quality evidence exists.

7. Handling information from the companies

Following a request for information, any 'commercial in confidence' data provided by a company and specified as such will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g., in brackets). Any academic-in-confidence data provided will be highlighted in yellow and underlined. Only information received by 15 July 2022 will be considered for inclusion in the assessment report.

8. Competing interests of authors

None

9. References

1. Morley RL, Sharma A, Horsch AD, Hinchliffe RJ. Peripheral artery disease. BMJ. 2018;**360**:j5842.

2. Pabon M, Cheng S, Altin SE, Sethi SS, Nelson MD, Moreau KL, et al. Sex Differences in Peripheral Artery Disease. Circ Res. 2022;**130**(4):496-511.

3. Shabani Varaki E, Gargiulo GD, Penkala S, Breen PP. Peripheral vascular disease assessment in the lower limb: a review of current and emerging non-invasive diagnostic methods. Biomed Eng Online. 2018;**17**(1):61.

4. Aung PP, Maxwell HG, Jepson RG, Price JF, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. Cochrane Database Syst Rev. 2007;**2007**(4):Cd000123.

5. Crawford F, Welch K, Andras A, Chappell FM. Ankle brachial index for the diagnosis of lower limb peripheral arterial disease. Cochrane Database Syst Rev. 2016;**9**(9):Cd010680.

6. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. Circ Res. 2015;**116**(9):1509-26.

7. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;**45 Suppl S**:S5-67.

8. Leng GC, Lee AJ, Fowkes FG, Whiteman M, Dunbar J, Housley E, et al. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. Int J Epidemiol. 1996;**25**(6):1172-81.

9. 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. 2001;**286**(11):1317-24.

10. Fowkes FG, Aboyans V, Fowkes FJ, McDermott MM, Sampson UK, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. Nat Rev Cardiol. 2017;**14**(3):156-70.

11. National Institute for Health and Care Excellence. Peripheral arterial disease: diagnosis and management [CG147]. 2012. Available from: https://www.nice.org.uk/guidance/cg147 (Accessed 14 March 2022).

12. Guest JF, Fuller GW, Vowden P. Cohort study evaluating the burden of wounds to the UK's National Health Service in 2017/2018: update from 2012/2013. BMJ Open. 2020;**10**(12):e045253.

13. National Wound Care Strategy Programme. Recommendations for Lower Limb Ulcers. 2020. Available from: https://www.nationalwoundcarestrategy.net/wp-content/uploads/2021/04/Lower-Limb-Recommendations-WEB-25Feb21.pdf (Accessed 14 March 2022).

14. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. Cochrane Database Syst Rev. 2012;**11**(11):Cd000265.

15. Callam MJ, Harper DR, Dale JJ, Ruckley CV. Arterial disease in chronic leg ulceration: an underestimated hazard? Lothian and Forth Valley leg ulcer study. Br Med J (Clin Res Ed). 1987;**294**(6577):929-31.

16. Nelzén O, Bergqvist D, Lindhagen A. Leg ulcer etiology--a cross sectional population study. J Vasc Surg. 1991;**14**(4):557-64.

17. Humphreys ML, Stewart AH, Gohel MS, Taylor M, Whyman MR, Poskitt KR. Management of mixed arterial and venous leg ulcers. Br J Surg. 2007;**94**(9):1104-7.

18. Bui UT, Finlayson K, Edwards H. Risk factors for infection in patients with chronic leg ulcers: A survival analysis. Int J Clin Pract. 2018;**72**(12):e13263.

19. Callam MJ, Ruckley CV, Dale JJ, Harper DR. Hazards of compression treatment of the leg: an estimate from Scottish surgeons. Br Med J (Clin Res Ed). 1987;**295**(6610):1382.

20. Danieluk A, Chlabicz S. Automated Measurements of Ankle Brachial Index: A Narrative Review. J Clin Med. 2021;**10**(21).

21. National Institute for Health and Care Excellence. How should I interpret ankle brachial pressure index (ABPI) results? 2021. Available from: https://cks.nice.org.uk/topics/leg-ulcer-venous/diagnosis/interpretation-of-abpi/ (Accessed 14 March 2022).

22. Scottish Intercollegiate Guidelines Network. SIGN 120 Management of chronic venous leg ulcers. Edinburgh: SIGN; 2010. Available from: https://www.sign.ac.uk/media/1058/sign120.pdf.

23. The Lymphoedema Framework. Best Practice for the Management of Lymphoedema. International consensus. London: MEP Ltd; 2006. Available from: https://www.lympho.org/wp-content/uploads/2021/09/Best_practice.pdf.

24. Mixed aetiology leg ulcers. 2006. Available from: https://www.nursingtimes.net/archive/mixed-aetiology-leg-ulcers-18-04-2006/ (Accessed 31 March 2022).

25. European Wound Management Association. Understanding compression therapy. London: Medical Education Partnership Ltd; 2003. Available from: https://ewma.org/fileadmin/user_upload/EWMA.org/Position_documents_2002-2008/Compression.pdf.

26. Grothier L. Leg ulcer management guidelines. Colchester, UK: Provide; 2015. Available from: https://www.legulcerforum.org/downloads/LUF_Leg_Ulcer_Clinical_Guidelines_15.pdf.

27. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;**155**(8):529-36.

28. Yang B, Mallett S, Takwoingi Y, Davenport CF, Hyde CJ, Whiting PF, et al. QUADAS-C: A Tool for Assessing Risk of Bias in Comparative Diagnostic Accuracy Studies. Ann Intern Med. 2021;**174**(11):1592-9.

29. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: [updated March 2011. London: The Cochrane Collaboration, 2011. Available from: http://handbook-5-1.cochrane.org/.

30. Centre for Reviews and Dissemination. Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care. York: 2009. Available from: www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf

31. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. Journal of Clinical Epidemiology. 1998;**51**(12):1235-41.

32. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of Epidemiology & Community Health. 1998;**52**(6):377-84.

33. Jackson R, Ameratunga S, Broad J, Connor J, Lethaby A, Robb G, et al. The GATE frame: critical appraisal with pictures. Evidence Based Medicine. 2006;**11**(2):35-8.

34. Deeks J, Bossuyt P, Gatsonis C. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0.0: 2013. Available from: https://methods.cochrane.org/sdt/handbook-dta-reviews

35. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol. 2005;**58**(10):982-90.

36. Schuetz GM, Schlattmann P, Dewey M. Use of 3x2 tables with an intention to diagnose approach to assess clinical performance of diagnostic tests: meta-analytical evaluation of coronary CT angiography studies. BMJ. 2012;**345**:e6717.

37. National Institute for Health and Care Excellence. NICE Diagnostic Assessment Programme manual. London/Manchester: 2011. Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-diagnostics-guidance/Diagnostics-assessment-programme-manual.pdf.

Appendix 1 Literature search strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to March 14, 2022>

1	Peripheral Arterial Disease/
2	(("Peripheral Arter*" adj3 Disease?) or PAD).tw,kw.
3	Intermittent Claudication/
4	(Intermittent adj3 Claudication).tw.
5	arterial occlusive diseases/ or arteriosclerosis/ or atherosclerosis/
6	("lower extremity arter* disease" or "lower limb arter* disease").tw,kw.
7	1 or 2 or 3 or 4 or 5 or 6 [PAD]
8	Ankle Brachial Index/
9	((brachial or ankle or arm) adj4 (index or pressure)).tw,kw.
10	(ABPI or ABI or AAI).tw,kw.
11	8 or 9 or 10 [ABPI]
12	Oscillometry/
13	plethysmography/ or photoplethysmography/ or plethysmography, impedance/
14	(Oscillometr* or plethysmograph* or photoplethysmograph*).tw,kw.
15	automat*.tw,kw.
16	12 or 13 or 14 or 15 [automated measurement]
17	(BlueDop or MESI or WatchBP or Microlife or Dopplex or Huntleigh or BOSO).tw. [devices]
18	7 and 11 and 16 and 17