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# Protocol for a prospective observational diagnostic study: intraoperative simultaneous limb pressure monitoring (INSTANT) study

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## ABSTRACT

**Introduction** Peripheral vascular disease (PVD) is a condition caused by arterial blockages causing inadequate blood flow, resulting in pain and gangrene of the legs. Endovascular therapy, such as angioplasty, can be used to treat PVD, however, the operator feedback during surgery is primarily anatomic based on the angiogram. Because physiologic blood perfusion can be difficult to determine based on anatomic images, we propose introducing physiological measurements into the operating room. This study will investigate whether the change in intraoperative monitoring of haemodynamic measurements such as the Toe-Brachial Index during endovascular surgery for lower extremity atherosclerotic PVD is associated with clinical outcomes such as major adverse limb events (MALEs).

**Methods and analysis** This study will be a prospective, operator-blinded and blinded endpoint adjudicated observational diagnostic cohort study. A total of 80 legs will be enrolled in the study. Ankle and toe blood pressures will be measured non-invasively at predetermined time points before, during and after surgery, and we will assess associations between changes in intraoperative pressure measurements and postoperative clinical and haemodynamic outcomes. The primary outcome will be MALE within 1 year, and secondary outcomes include follow-up pressure measurements, vessel patency, reintervention, clinical staging improvement, amputation and death.

**Ethics and dissemination** Regional hospital ethics approval has been granted (Ottawa Hospital Research Institute - Research Ethics Board, Protocol 20180656–01H). On completion of data analysis, the study will submitted for presentation at international vascular surgical society meetings, in addition to submission for publication in publicly accessible medical journals.

**Trial registration number** NCT03875846

## Strengths and limitations of this study

- ► Novel application of intraoperative physiological monitoring using ankle and toe blood pressure during revascularisation procedures.
- ► Prospective, operator-blinded and blinded endpoint adjudicated.
- ► Observational cohort study.
- ► Resource intensive pressure measurement.

## INTRODUCTION

Peripheral vascular disease (PVD) is a condition caused by arterial blockages causing inadequate blood flow, resulting in pain and gangrene of the legs. The prevalence of PVD in the North American general population over 50 years of age is estimated at 17.4%, and is rising in association with the increasing prevalence of diabetes.[1] While bypass surgery is reserved for patients with severe forms of PVD, the minimally invasive options of angioplasty ('endovascular surgery') is emerging as the treatment of choice for most patients with PVD. The annual rate of endovascular peripheral vascular interventions in the USA Medicare population has risen to 419.6 per 100 000 Medicare beneficiaries.[2] Angioplasty is the foundational treatment of endovascular therapy, which may be augmented by treatments such as stenting. Unfortunately, the 2-year patency of balloon angioplasty for PVD has been poor, reported between 50% and 80%, depending on lesion location and characteristics.[3] Subsequently, the 1-year amputation rate despite endovascular revascularisation has been reported as high as 32% in patients with lower leg critical limb ischaemia.[4] This high failure rate has prompted investigation into the predictors of failure, and potential solutions to optimise the success rate of revascularisation.

One of the most significant predictors of clinical success following endovascular surgery for PVD is the postprocedure Ankle-Brachial Index (ABI).[5] This measurement is performed by applying a blood pressure cuff at the level of the lower leg ('Ankle Pressure') and the arm. The ABI is a ratio of the blood pressure at the ankle when compared with the arm. Similarly, a smaller cuff around the great toe can determine the absolute toe pressure, which can

also be used to calculate the Toe-Brachial Index (TBI). The change in ABI following endovascular surgery can be detected a day after the procedure, and remains stable throughout the month following the procedure.[6] While the ABI is commonly used for monitoring haemodynamic improvement after endovascular surgery, postoperative surveillance TBI has been demonstrated to have a significantly stronger correlation with clinical outcomes such as major adverse limb events (MALE).[7] 'MALE' is defined as a composite outcome of clinically driven target limb reintervention and major amputation.[8] While the TBI is an important marker for postoperative outcomes, attempting these measurements during the procedure has never been reported.

Other postoperative markers of limb perfusion have also been investigated. MR arterial spin labelling correlates with postoperative ABI and clinical outcomes.[9] Furthermore, some authors have investigated markers of limb perfusion during surgery, finding correlation between postoperative ABI and intraoperative two-dimensional perfusion angiography[10] and indocyanine green intra-arterial injection.[11] Other methods, such as laser Doppler,[12] near-infrared spectroscopy,[13 14] transcutaneous oxygen saturation[15] and micro-oxygen sensors,[16] have demonstrated delayed feedback of perfusion that would not be rapid enough to guide intraoperative decision making.

The potential utility of limb blood pressure to predict clinical outcomes after endovascular revascularisation presents several opportunities. Measurement of limb blood pressure is relatively simple to perform intraoperatively, particularly during endovascular procedures. The intraoperative use of ankle or toe blood pressure measurement has never been described. Therefore, while limb blood pressure measurements may be significant predictors of outcomes, the current practice of waiting to measure the limb pressure after surgery may miss opportunities to guide intraoperative decision-making.

Currently, the primary intraoperative feedback used to determine procedural success is the anatomic appearance of the angiogram on completion of the procedure. While an angiogram may depict the improvement of focal arterial narrowing, it does not provide physiological feedback to the operator. Small vessel disease or tandem lesions may instead be the primary culprit of the PVD, and would not be demonstrated adequately by the angiogram. Consequently, an anatomically significant lesion may not be haemodynamically significant, resulting in a falsely reassuring angiogram. Because limb pressure measurements encompass these variables that are not accounted for by angiogram, limb pressure measurement could be more predictive of procedural success than angiogram. This study investigates the diagnostic association between intraoperative non-invasive limb blood pressure measurement and postoperative outcomes. If applying limb blood pressure monitoring into the operating room is predictive of outcomes, the results of this study will guide further investigation into using instant blood pressure feedback to guide intraoperative decision making and ultimately improve the success of endovascular revascularisation.

## OBJECTIVES

### Primary objective

The primary objective of this investigation is to determine if the magnitude of change of intraoperative TBI during endovascular revascularisation (preangioplasty and postangioplasty) for atherosclerotic PVD is associated with freedom from MALEs within 1-year postprocedure.

Intraoperative TBI change is defined as the difference between the preintervention and postintervention time point measurements, which are described in detail under the 'Data Collection' heading. MALE is defined as a composite outcome of major amputation above the ankle, major reintervention in the form of catheter-directed thrombolysis, open bypass or thrombectomy.[17]

### Secondary objectives

In addition to a the magnitude change in intraoperative TBI, we will also evaluate the association of the binary intraoperative perfusion marker change on symptom improvement, major and minor amputation, target lesion/vessel/limb reintervention, target vessel patency and association between intraoperative and postoperative measurements.

Beyond analysing TBI, we will analyse other intraoperative measures of change in limb perfusion including ABI, absolute toe pressures and absolute ankle pressures. All measures of intraoperative changes perfusion will be calculated as the difference between the preintervention and postintervention time point measurements. Ideal acceptable threshold improvements in intraoperative TBI and ABI will be determined using Youden's method, to potentially use as a clinical decision rule in further research. The study will also report feasibility measures including rate of enrolment and reported anticipated or unanticipated disruptions to patient flow during intraoperative data collection.

## METHODS AND ANALYSIS

### Study design

This study will be a prospective observational cohort study. The surgical operators will be blinded to intraoperative pressure measurements. All radiographic and postoperative clinical endpoints will be assessor blinded.

### Setting

Patients undergoing treatment by the Division of Vascular Surgery at The Ottawa Hospital, Civic Campus. All patients will be under the care of the Vascular Surgery Division, both inpatients and outpatients. All outpatient limb pressure measurements will have been performed at the Vascular Ultrasound Diagnostic Laboratory, and all endovascular procedures and intraoperative limb pressure measurements performed in the operating

theatres of the Civic Campus. We will leverage our status as the only vascular surgical service in the medical region (Champlain LHIN) to maximise capture of outcomes following the index procedure.

## Study population

### Inclusion criteria

- Patients undergoing elective or semiurgent endovascular procedures on de novo lesions of the aorta, iliac, femoral, popliteal or tibial arteries.
- Symptomatic, atherosclerotic PVD.
- Age 18 years old or greater.
- Detectable toe pressure.

### Exclusion criteria

- Concurrent hybrid open procedure during endovascular revascularisation requiring vascular clamping for any period of time, such as endarterectomy.
- Prior open vascular surgery performed on the affected leg.
- Emergent intervention for acute limb ischaemia, defined as symptoms lasting less than 14 days.
- Non-femoral vascular access.

### Recruitment

Recruitment for this study will be performed just after consent for the procedure is obtained, by notification of the attending vascular surgeon.

## Variables

### Baseline characteristics

- Age.
- Sex.
- Smoking status.
- Diabetes.
- Hypertension.
- Dyslipidaemia.
- Antiplatelet use.
- Anticoagulant use.
- Statin use.
- Chronic kidney disease (estimated Glomerular Filtration Rate (eGFR) <60).
- Dialysis dependence.
- Trans-Atlantic Inter-Society Consensus (TASC) Classification.[18]
- Rutherford's Classification of PVD.[19]
- WIFi classification.[8]

### Preoperative limb pressures

- Ankle pressure.
- Toe pressure.
- Brachial pressure.
- ABI.
- TBI.

### Procedural characteristics

- Vessel(s) of intervention.
- Anatomic level (iliac, femoropopliteal and infrageniculate).
- Severity of stenosis.
  - <50%, 50%–75% or >75% stenosis.
  - Complete occlusion.
- Residual stenosis.
- Adjunctive procedures.
  - Drug-eluting balloon.
  - Stenting.
    - Balloon expandable.
    - Self-expanding.
    - Bare-metal.
    - Covered.
  - Thrombectomy.
  - Atherectomy.

### Intraoperative perfusion markers of interest

- Ankle pressure.
- Toe pressure.
- Brachial pressure.
- ABI.
- TBI.

## Primary outcome

The primary outcome is freedom from MALE within 1-year postintervention. MALE is defined as a composite outcome of major amputation above the ankle, major reintervention in the form of catheter-directed thrombolysis, open bypass or thrombectomy.

## Secondary outcomes

All clinical outcomes are assessed within 1-year postindex procedure, and haemodynamic outcomes assessed at 1–3 months postindex procedure.

- Improvement in Rutherford's Classification of PVD.
- Amputation.
  - Minor (toe(s) or foot to the ankle).
  - Major (above the ankle)
- Minor Amputation (toe(s) or foot).
- Major amputation (above the ankle).
- Target limb reiIntervention.
  - Endovascular.
  - Bypass.
  - Thrombectomy.
  - Thrombolysis.
- Target vessel reintervention.
- Target lesion reintervention.
- Target vessel patency.
  - Primary (absence of target vessel occlusion or restenosis >50%).
  - Primary assisted (patency requiring assistance of subsequent procedure to maintain patency of target vessel).
  - Secondary (patency requiring assistance of subsequent procedure to restore patency of target vessel).
- Mortality
- Amputation-free survival.
- Correlation between immediate postoperative limb pressure and 1–3 months follow-up limb pressure measurement.

### Feasibility outcomes

- Enrolment.
  - Enrolment rate.
  - Consent rate for subjects approached for study participation.
- Data capture.
  - Rate of complete intraoperative data capture of consenting subjects.
  - Postoperative subject involvement retention rate.
- Disruptions to patient flow.
  - Total time of procedures.
  - Reported unexpected disruptions.

### Sample size

Due to the nature of investigating a novel technique, there is limited established evidence to guide expected results for a sample size calculation. The most closely related published data are found in a subgroup analysis of the IN.PACT DEEP trial, which followed patients for 12 months after infrainguinal angioplasty.[7] In patients who experienced any improvement of TBI immediately postoperatively, this study identified an HR of 0.15 (95% CI 0.04 to 0.57) of 'MALE' within 1 year, defined as major limb amputation above the level of the ankle, or major target lesion revascularisation in the form of thrombolysis, thrombectomy or bypass. The study also found a sampling distribution ratio of patients demonstrating an improvement in TBI to no improvement in TBI of 2.14. On survey of regional attending vascular surgeons to depend on an intraoperative monitoring system, an HR of 0.15 would be appropriate as a minimum to guide intraoperative decision-making.

This study includes patients undergoing endovascular procedures for a spectrum of symptomatic PVD, including those with claudication and critical limb ischaemia. The primary outcome of this study will be defined as MALE. The expected 1-year event rate of MALE is higher in subjects with critical limb ischaemia (20.5%[7] vs subjects with claudication 3.2%).[20] Based on a recent 10-year audit of endovascular procedures performed at the investigational centre (The Ottawa Hospital, Civic Campus) the expected proportion of eligible subjects with critical limb ischaemia (vs claudication) is 0.625. Therefore, we will need to calculate an overall expected event rate based on the relative proportion of each disease severity, in addition to their respective event rates. This calculation can be seen in table 1, and ultimately, the overall expected event rate is 14%. The Division of Vascular Surgery at The Ottawa Hospital is the sole vascular surgical provider for the region, therefore, the expected lost to follow-up is minimal and estimated at less than 5%. The anticipated rate of inclusion of bilateral legs of the same subject is less than 20%, and therefore, the expected loss of analytical power due to robust sandwich estimate cluster modelling is minimal and will be accounted for in our inflation adjustment of 10%. In light of an alpha of 0.05, beta of 0.20, buffer for lost to follow-up and cluster modelling of 10%, sampling distribution of 2.14:1, HR of 0.15, a total of 80 legs will be enrolled.

**Table 1** Sample size calculation

| Variable | Value |
|---|---|
| Alpha | 0.05 |
| Power | 0.80 |
| Sampling distribution | 2.14:1 |
| Overall event probability | 0.140 |
| Critical limb ischaemia | 0.205 |
| Proportion of subjects with critical limb ischaemia | 0.625 |
| Claudication | 0.032 |
| Proportion of subjects with claudication | 0.375 |
| Calculation of overall event probability | (0.205*0.625)+(0.032*0.375) |
| HR | 0.15 |
| Inflation: loss to follow-up, cluster analysis | 10% |
| **Total sample size** | **80 legs** |

### Planned analyses

The unit of analysis will be individual legs; one subject may contribute two eligible legs to the study. Therefore, all analyses will account for clusters of legs to each subject. Survival analysis of the primary outcome (MALE) as a function of the magnitude of improvement of perioperative TBI will be performed with Cox Proportional Hazards, using robust sandwich estimate cluster modelling, competing risk adjustment and adjusting for preoperative Rutherford's classification, anatomic level of disease and discrepant baseline characteristics. An unadjusted univariate log rank test will also be reported.

The following time-to-event secondary outcomes compared between those with positive limb pressure change and those without improvement or negative change will be analysed using Cox proportional hazards with generalised estimating equations for clustering, competing risk adjustment and adjustments for preoperative Rutherford's classification and anatomic level of disease: major and minor amputation, reintervention, target vessel patency, mortality and amputation-free survival. An unadjusted univariate log rank test will also be reported.

Logistic regression with generalised linear mixed model, clustering by patient and adjusted for preoperative Rutherford's classification and anatomic level of disease, will be used to analyse the binary outcome of any symptomatic improvement based on the postoperative Rutherford's classification. An unadjusted univariate logistic regression will also be reported.

Using ROC curves developed by models correlating MALE based on intraoperative change in toe and ankle pressures, the ideal threshold will be identified using Youden's method. This new threshold will then be used to replicate the primary analysis with binary toe and ankle pressure thresholds.

**Table 2** Schedule of assessments. see below for specific time point definitions

| | | Time point | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Preoperative | Perioperative | | | | Postoperative | |
| | | Recruitment | Preprocedure | Preintervention | Postintervention | Postprocedure | 1-month follow-up | 0–12 months follow-up |
| Clinical | Baseline characteristics | X | | | | | | |
| | Rutherford's Score | X | | | | | | X |
| | Ipsilateral endovascular reintervention | | | | | | | X |
| | Ipsilateral open reintervention | | | | | | | X |
| | Minor amputation | | | | | | | X |
| | Major amputation | | | | | | | X |
| | Mortality | | | | | | | X |
| Pressures | Toe pressure | | X | X | X | X | X | |
| | Ankle pressure | | X | X | X | X | X | |
| | Arm pressure | | X | X | X | X | X | |
| Radiographic | Severity of lesion stenosis | X | | | | X | | |
| | Society for Vascular Surgery (SVS) runoff score | X | | | | X | | |
| | Primary patency | | | | | | | X |
| | Primary assisted patency | | | | | | | X |
| | Secondary patency | | | | | | | X |
| | Feasibility | X | | | | X | X | X |

Time point definitions. Preprocedure: lying supine, on day of procedure, prior to arterial puncture. Preintervention: balloon deflated but while catheter across lesion. Postintervention: balloon deflated but while catheter across lesion. Postprocedure: lying supine, after all catheters/sheaths are removed, and after manual pressure applied to the puncture site has been released.

The correlation between immediate postoperative toe and ankle pressure measurements and follow-up pressure measurements will be assessed using Pearson's coefficient, Intraclass correlation and Bland-Altman plots. We will repeat these correlation analyses when comparing preprocedure and preintervention measurements, as well as a comparison of postintervention and postprocedure measurements (table 2). In addition, analysis of the variability in measurement of both preoperative and postoperative values will be performed. As these measurements are repeated three times during both of these time points, we will report both SD and SE of the mean.

Planned subgroup analyses include stratification for the three vascular levels (iliac, femoropopliteal and tibial), critical limb ischaemia versus claudication, stenting vs angioplasty alone and preoperative TASC II classification.

Feasibility outcomes, including enrolment, consent, intraoperative data capture and postoperative retention rates, will be reported as absolute values and fractions. Qualitative descriptions of reported unexpected disruptions to patient flow will be described. Total operative times will be presented alongside the allocated timeframe for the procedures. No statistical analyses are planned for feasibility outcomes.

## Missing and incomplete data

If no clinical contact is made with a subject following the index procedure, the subject will be considered lost to follow-up and will be excluded from analysis. Missing postoperative pressure measurements due to missed appointments will be addressed with mixed model repeated measures imputation. Missing postoperative pressure measurements due to amputation or mortality will be excluded from correlation analyses.

The primary outcome, MALE, is a composite outcome that accommodates potential intercurrent events such as reintervention and amputation, however, it does not include mortality. In the case of mortality, this will be

labelled as a competing risk and will be accommodated by the survival analyses models. The secondary outcomes will use a treatment policy strategy, where the variable will be included regardless of intercurrent events. However, specific intercurrent events of amputation, mortality or in certain outcomes intercurrent bypass surgery, will be included as competing risks in the survival analysis models.

## STUDY ADMINISTRATION

### Feasibility and study duration

Between the division of vascular surgery and the division of radiology, approximately six lower extremity endovascular revascularisation procedures per week are performed at the Civic Campus. Approximately half of these cases are expected to be eligible based on an audit of the prior year. With a target enrolment of 80 legs, enrolment could be achieved within 7 months if all cases are enrolled. The enrolment rate of eligible cases is expected to be moderate, given the non-invasive nature of this study. In total, 11 months have been allocated to study enrolment.

### Data sources

Baseline and postoperative follow-up clinical data will be collected through vOACIS–PROD (V.r7.3.0_20130320). vOacis is the central electronic medical record system used by The Ottawa Hospital, and is where all vascular surgery clinical appointment and operative notes are documented. Perioperative data will be the only data collected in addition to standard medical care. This is the only data source that is a result of study member interaction with the study subjects.

### Data collection

After enrolment into the trial, the study administrator will collect baseline data based on relevant notes in vOacis as described above. Only the principal investigator and study coordinator will have access to the password and data collection forms.

Perioperative data collection will occur on the day of surgery. An automated non-invasive blood pressure cuff (NIBP) will be placed around the patient's arm, and additional ankle and toe blood pressure cuffs will be placed around the patient's leg and great toe with a distal photoplethysmography recorder. Because only femoral vascular access will be considered in this study, the blood pressure cuffs below the knees will be separate from the operative field and will be covered by standard draping procedure to maintain sterility.

The ankle blood pressure cuff size will be a universal Hokanson SC12 straight segmental cuff, 13 cm x 85 cm. Toe blood pressure cuff size will be chosen as the cuff width closest to 20% wider than the toe diameter. Available toe pressure cuffs are Hokanson UPC2.5 2.5 cm x 12 cm and Hokanson UPC3.3 3.3 cm x 12 cm. The FalconPro Viasonix machine will be used for NIBP measurements, connected to a FalconQuad machine for Viasonix Disk PPG sensor input.

Prior to commencement of the procedure, the ankle and toe blood pressure of the affected limb(s) in addition to the blood pressure of the arms will be measured. If any regional anaesthetic such as epidural or spinal analgesia is to be administered, the preoperative measurement must be taken at minimum 15 min after anaesthetic administration to allow for onset of sympathetic blockade vasodilation. Preprocedure and postprocedure pressure measurements will be repeated three times at least 5 min apart to assess measurement variability.

After vascular access is obtained and the intra-arterial vascular sheath has been inserted, another set of blood pressure measurements will be obtained. This is because the physical presence of the intra-arterial instruments may affect distal leg and toe pressures. Following angioplasty, a repeat set of pressure measurements will be obtained prior to removal of intra-arterial instruments. The postintervention measurements will be repeated after repeated endovascular treatment on the same leg during the procedure, such as multilesion angioplasty, stent or atherectomy. Finally, after the completion of the procedure and removal of all intra-arterial instruments, a final set of postoperative measurements will be obtained.

If an ulcer or infection precludes great toe pressure measurement, an alternate toe will be used to measure toe pressure. If the baseline ABI or TBI is greater than 1.5, we will infer incompressible vessels and deem the measurement unreliable.

Postoperatively, patients will follow routine follow-up scheduled clinic and ultrasound appointments at 1–3 months, which will not involve any active study intervention. The angiograms will be de-identified and presented to a blinded investigator to determine procedural anatomic success. Data will be collected from these images and appointments, during which the observer collecting postoperative data will remain blinded to the intraoperative results. On completion of follow-up data collection, the datasets will be frozen and merged for analysis. The schedule of assessments is presented in table 2.

Subject retention will be primarily promoted by the design of the study, which completes intraoperative measurements in a single and non-intrusive patient encounter during surgery. Postoperatively, the study leverages the Ottawa Division of Vascular Surgery as the only vascular surgical service in the public health region, to ensure complete data capture of postoperative outcomes. Because there is no further study-specific subject contact after surgery, we anticipate high postoperative retention rates. Subjects will be encouraged to attend all postoperative appointments at the time of enrolment, but will not be contacted by study personnel to promote postoperative appointment adherence.

### Blinding

The surgical operator, operating assistant, scrub nurse and any other member participating in the patient's

circle of care will be blinded from the intraoperative results of this study. The operators will rely on standard of care intraoperative feedback mechanisms such as intraoperative angiogram to guide the procedures. This blinding applied both to the intraoperative period as well as the postoperative period, such that the intraoperative pressure results will not factor into postoperative decision-making by members of the subject's circle of care.

As well as blinding clinicians involved in the administration of healthcare, all ultrasound technologists responsible for postoperative blood pressure measurements will be blinded from the intraoperative limb pressure results. Finally, the intraoperative pressure measurement data collection file will be 'frozen' and provided to our statistician before any postoperative clinical outcome data collection is performed. The study official who will then perform postoperative outcome data collection will be separate from the study members who performed intraoperative pressure measurements, and will be blinded from these results while performing postoperative outcome data collection.

### Data monitoring and management

This is a single-centre study and all data will be stored locally. All intraoperative data collection will initially occur on hard copy datasheets, which will be stored in a locked container in a locked room within the study hospital, which is only accessible by the study member performing intraoperative data measurement. Each limb is assigned a 'study-specific identification number', which will be used to link data for analysis.

All intraoperative data will be transferred to a password-protected spreadsheet locally, which is held on The Ottawa Hospital server and will be updated until recruitment is complete, at which time the intraoperative dataset will be 'frozen' and sent to a statistician. Double data entry will be performed by a second study member will separately repeat data entry from the paper form to another password-protected spreadsheet, which will also be sent to the statistician to ensure accurate data coding between the two members.

Independent source verification will be performed by the statistician, by reviewing at random 20% of all paper case report forms. In addition, the intraoperative pressure data will be screened for outliers by flagging any pressure measurement value falling outside 2 SD of the baseline measurement for review. The statistician will have access to paper case report forms to ensure accuracy of data entry in these cases.

Postoperative outcome assessment will not start until recruitment is complete, and will be performed by two additional study members who will not have access to intraoperative results. Double data entry will be performed by each member into independently password-protected electronic datasets for all postoperative outcomes including the primary outcome of MALE. On completion of postoperative outcome measurements, the outcome datasets will also be available to the statistician for final analysis and confirmation of accuracy between the double-entry files. At any point, discrepancy between double-entry files will be brought to the attention of the principal investigator for resolution.

The individual study members conducting intraoperative data collection will have separate password access to their individual files, in addition to the principal investigator and local ethics board who have access to all files as required by the ethics committee. This is designated as a minimal-risk study, and there will be no interim analysis for the purposes of safety monitoring. Due to the relatively short duration of the study, these passwords will remain constant during the study unless a security breach is suspected. All paper and electronic datasets will be retained for 10 years following completion of the study.

### Access to data

The Ottawa Hospital Research Institute - Research Ethics Board (OHRI-REB) will have access to anonymised data at their discretion, as per REB policy. However, no third party investigators or corporate bodies will have access to study data prior to synthesis and dissemination.

### Confidentiality

All data and records generated during this study will be kept confidential in accordance with institutional and OHRN-REB policies. The investigators will not use such data and records for any purpose other than conducting the study. Only necessary personal identification data will be collected, and deleted or destroyed at the earliest feasible time. Data will be collected and stored securely and anonymously in password protected files and on a hospital server, as described above.

### Study timeline

Enrolment start date: October 2018.
Enrolment stop date: August 2019.
Data collection stop date: August 2020.
Submission for publication: September 2020.

## ETHICS AND DISSEMINATION

### Risk assessment

The only procedure affecting study subjects beyond the standard of care is a benign NIBP measurement of the lower extremities, which they already routinely receive serially in the same fashion before and after surgery at ultrasound appointments. On review of literature, there have been no reported adverse events resulting from blood pressure measurement of the lower extremity. However, cuff inflation at the ankle immediately following a lower tibial intervention such as angioplasty may theoretically encourage vessel thrombosis; the ankle cuff will not be inflated following any lower tibial interventions. The transiently inflated blood pressure cuff of the leg may be uncomfortable for the duration of inflation, similar to blood pressure measurement of the arm. This will be minimised by inflating the lower extremity blood

pressure cuffs to appropriate pressures standardised by the upper extremity inflations. The blood pressure cuffs will be applied several feet away from the operative field, addressing any potential compromise of surgical field sterility.

## Reportable events

Any suspected (confirmed or unconfirmed) breach in confidentiality will be immediately reported to the OHRI-REB. This will include coordination with the review board for rapid notification of the patient(s) in question.

Any significant interruption in the flow of the operating theatre may be reported by any member of the operating theatre to the OHRI-REB. The study protocol, in addition to primary investigator, study coordinator and OHRI-REB contact information, will be posted and freely accessible in all vascular surgical operating theatres to ensure study transparency.

The study subjects will also be encouraged to report any irregular events to the study coordinator, principal investigator and/or OHRI-REB as described in the consent forms.

## Consent

Consent for this study is necessary as there are measurements that will occur beyond the standard of care. These measurements, while they qualify as minimal risk, will be fully explained to the subjects prior to obtaining consent. The access to electronic health records will also be discussed. The coordinator obtaining consent will have no direct involvement in the medical care of the subject.

## Protocol amendments

All protocol amendments will require REB approval, in addition to principal investigator and study coordinator consensus.

## Patient and public involvement

There were no funds or time allocated for patient and public involvement, however, we have invited patients to help us develop our dissemination strategy.

## Dissemination

Following completion of data analysis, the study will be synthesised and submitted for presentation at national and international vascular surgical society meetings, in addition to submission for publication in publicly accessible medical journals. All publicly presented and published data will describe the cohorts as a whole anonymously and will not include any direct identifiers.

## Limitations

The eligibility criteria may unintentionally exclude subjects with a history of unrelated venous procedures such as great saphenous venous stripping, and include aortic stenting for occlusive disease, which is a relatively unique and rare procedure. Although these are anticipated to affect only a small subset of patients and will likely not have a differential effect, these eligibility criteria were established at the time of enrolment and will not be changed during the course of the study to maintain integrity.

The original protocol guiding enrolment of the majority of subjects did not explicitly state that both arm blood pressures will be measured and that the highest systolic pressure will be used for calculations of pressure indices. This is the standard protocol for assessment of ABI and TBI, and this method of determining the arm laterality for use in calculations has been performed in all instances, but has not been explicitly described in the protocol until a revision on 21 June 2019.

**Contributors** MR and PJ contributed to the concept of designing this study. MR and GAW defined the study design and analytic plan. MR, PJ and GAW all contributed to writing and critical review of the manuscript.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** This study has received OHRI-REB approval (Protocol 20180656–01H), which was most recently provided following an amendment on 10 January 2019.

**Provenance and peer review** Not commissioned; externally peer reviewed.



## REFERENCES

1. Collins JS. Gender and peripheral vascular disease. *J Am Board Fam Med* 2006;19:132–40.
2. Jones WS, Mi X, Qualls LG, *et al*. Trends in settings for peripheral vascular intervention and the effect of changes in the outpatient prospective payment system. *J Am Coll Cardiol* 2015;65:920–7.
3. Lazaris AM, Tsiamis AC, Fishwick G, *et al*. Clinical outcome of primary infrainguinal subintimal angioplasty in diabetic patients with critical lower limb ischemia. *J Endovasc Ther* 2004;11:447–53.
4. Feiring AJ, Krahn M, Nelson L, *et al*. Preventing leg amputations in critical limb ischemia with below-the-knee drug-eluting stents: the paradise (preventing amputations using drug eluting stents) trial. *J Am Coll Cardiol* 2010;55:1580–9.
5. Keeling AN, Khalidi K, Leong S, *et al*. Subintimal angioplasty: predictors of long-term success. *J Vasc Interv Radiol* 2009;20:1013–22.
6. Allouche-Cometto L, Leger P, Rousseau H, *et al*. Comparative of blood flow to the Ankle-brachial index after iliac angioplasty. *Int Angiol* 1999;18:154–7.
7. Hammad TA, Zeller T, Baumgartner I, *et al*. Analysis of IN.PACT deep trial on the association between changes in perfusion from pre- to postrevascularization and clinical outcomes in critical limb ischemia. *Catheter Cardiovasc Interv* 2017;90:986–93.
8. Mills JL, Conte MS, Armstrong DG, *et al*. The Society for vascular surgery lower extremity threatened limb classification system: risk stratification based on wound, ischemia, and foot infection (WIfI). *J Vasc Surg* 2014;59:220–34.
9. Grözinger G, Pohmann R, Schick F, *et al*. Perfusion measurements of the calf in patients with peripheral arterial occlusive disease before and after percutaneous transluminal angioplasty using MR arterial spin labeling. *J Magn Reson Imaging* 2014;40:980–7.
10. Hinrichs JB, Murray T, Akin M, *et al*. Evaluation of a novel 2D perfusion angiography technique independent of pump injections for assessment of interventional treatment of peripheral vascular disease. *Int J Cardiovasc Imaging* 2017;33:295–301.
11. Igari K, Kudo T, Uchiyama H, *et al*. Intraarterial injection of indocyanine green for evaluation of peripheral blood circulation

in patients with peripheral arterial disease. *Ann Vasc Surg* 2014;28:1280–5.
12. Hoffmann U, Schneider E, Bollinger A. Flow motion waves with high and low frequency in severe ischaemia before and after percutaneous transluminal angioplasty. *Cardiovasc Res* 1990;24:711–8.
13. Boezeman RPE, Becx BP, van den Heuvel DAF, *et al*. Monitoring of foot oxygenation with near-infrared spectroscopy in patients with critical limb ischemia undergoing percutaneous transluminal angioplasty: a pilot study. *Eur J Vasc Endovasc Surg* 2016;52:650–6.
14. Yu G, Shang Y, Zhao Y, *et al*. Intraoperative evaluation of revascularization effect on ischemic muscle hemodynamics using near-infrared diffuse optical spectroscopies. *J Biomed Opt* 2011;16:027004.
15. Qian S, Iwai T. Intraoperative evaluation of success and failure of vascular reconstruction by monitoring the transcutaneous partial pressure of oxygen. *Vasc Surg* 2000;34:483–90.
16. Montero-Baker MF, Au-Yeung KY, Wisniewski NA, *et al*. The First-in-Man "Si Se Puede" Study for the use of micro-oxygen sensors (MOXYs) to determine dynamic relative oxygen indices in the feet of patients with limb-threatening ischemia during endovascular therapy. *J Vasc Surg* 2015;61:1501–10.
17. Stoner MC, Calligaro KD, Chaer RA, *et al*. Reporting standards of the Society for vascular surgery for endovascular treatment of chronic lower extremity peripheral artery disease: Executive summary. *J Vasc Surg* 2016;64:227–8.
18. Jaff MR, White CJ, Hiatt WR, *et al*. An update on methods for revascularization and expansion of the TASC lesion classification to include below-the-knee arteries: a supplement to the Inter-Society consensus for the management of peripheral arterial disease (TASC II). *Vasc Med* 2015;20:343–57.
19. Hardman RL, Jazaeri O, Yi J, *et al*. Overview of classification systems in peripheral artery disease. *Semin Intervent Radiol* 2014;31:378–88.
20. Fashandi AZ, Mehaffey JH, Hawkins RB, *et al*. Major adverse limb events and major adverse cardiac events after contemporary lower extremity bypass and infrainguinal endovascular intervention in patients with claudication. *J Vasc Surg* 2018;68:1817–23.