Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	FlowMet-R Blood Flow Measurement for the Diagnosis of Peripheral Artery Disease (PAD) and Critical Limb Ischemia (CLI)
Study Product Name	FlowMet-R
Sponsor/Local Sponsor	Medtronic Vascular, Inc. 3576 Unocal Place Santa Rosa, CA 95403
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1. Glossary

Term	Definition
ABI	Ankle brachial index
AE	Adverse event
ATK	Above the knee
AUC	Area Under the (ROC) Curve
BTK	Below the knee
CCD	Charge coupled device
CDU	Color duplex ultrasound imaging
CI	Confidence interval
CLI	Critical limb ischemia
Cm	Centimeter
CMOS	Complementary Metal-oxide Semiconductor
CRF	Case report form
EDC	Electronic Data Capture
FDA	Food and drug administration
Hr	Hour
ICF	Informed consent form
IRB	Institutional review board
Nm	Nanometer
OHRP	Office of Human Research Protection
PAD	Peripheral artery disease
PPG	Photoplethysmography
ROC	Receiver operating characteristic

Term	Definition
SAE	Serious adverse event
TBI	Toe brachial index
US	United states

2. Synopsis

Title	FlowMet-R Blood Flow Measurement for the Diagnosis of Peripheral Artery Disease (PAD) and Critical Limb Ischemia (CLI)
Product Name	FlowMet-R
Sponsor	Medtronic Vascular, Inc. 3576 Unocal Place Santa Rosa, CA 95403
External Organizations	[redacted]
Investigation Purpose	The purpose of the investigation is to assess the efficacy of the FlowMet-R device in diagnosing PAD and CLI in patients scheduled for peripheral vascular examination. The results of the assessment of the FlowMet-R device will be compared to gold standard diagnostics including ABI, TBI, and Doppler Ultrasound.
Primary Objective(s) and/or Endpoint(s)s	The primary objective is to determine the efficacy of FlowMet-R measurements in diagnosing PAD and CLI in patients during initial visit, three month, and six month follow-up.
Secondary Objective(s) and/or Endpoint(s)	The secondary objectives are to determine the capability of the FlowMet-R in prognosis of requiring vascular intervention or amputation within three and six months following the initial visit. Additionally, to investigate the correlation between FlowMet-R measurements and peripheral artery stenosis. Finally, to assess the correlation between changes in ABI/TBI/Rutherford Classification and changes in FlowMet-R data between any two time points.
Study Design	Multi-center, non-randomized, longitudinal study with three and six month follow-up.
Sample Size	**PAD Cohort:** Cohort will consist of 240 limbs with PAD including a minimum of 54 limbs with claudication and a minimum of 100 limbs with CLI. All comers - any patient scheduled for peripheral vascular

	assessment who is not subject to exclusion may be approached for enrollment in the disease positive arm. Exclusion criteria are detailed in Section 8.4. This will include patients in the registry who have a planned endovascular or surgical intervention to address their PAD. **Healthy Cohort:** Cohort will consist of 160 control limbs. Any patient over 40 years old and without suspected PAD may be approached for enrollment in the healthy control arm. Healthy subjects may be enrolled from other departments within the clinic/hospital, can be from the local community, or can be actively recruited for participation (such as researchmatch.com or active volunteers). **Registry:** Patients diagnosed with PAD at baseline procedure who are scheduled to undergo an endovascular treatment of the lower limbs will be included in the registry data for this study. The registry will be established to record FlowMet-R measurements, angiographic films, and any additional relevant information immediately prior to, during, and immediately following peripheral vascular interventional procedures for enrolled patients.
Inclusion/Exclusion Criteria	**INCLUSION CRITERIA** **PAD Positive Cohort:** – Subject meets PAD positive criteria set forth in Section 8.4 – Subject is willing and able to provide informed consent – Subject is willing and able to comply with the study procedures – Subject is able to understand the study procedures – Subject is scheduled for vascular examination that includes noninvasive assessments as standard of care: ABI, TBI, and either a Duplex Ultrasound or Angiogram **Healthy Cohort:** – Subject is willing and able to provide informed consent – Subject is willing and able to comply with the study procedures – Subject is able to understand the study procedures – Subject has no history of positive PAD diagnosis and is not currently suspected of having PAD **EXCLUSION CRITERIA** **PAD Positive Cohort:** – Subject is under 40 or unable to consent

	– Subject has any medical condition, which, in the judgement of the Investigator and/or designee, makes the subject a poor candidate for the investigational study – Subject is excluded from analysis if no stenosis is found during Dopper Ultrasound, but Tibial disease is suspected and Tibial ultrasound is not able to be performed – Subject does not have a suitable finger to attach the FlowMet-R probe – Subject does not have a suitable 1st or 2nd digit to attach the FlowMet-R probe on the limb of interest – Subject has undergone revascularization within the last 90 days – Subject cannot lay safely in a supine position **Healthy Cohort Exclusion:** – Subject is under 40 or unable to consent – Subject has any medical condition, which, in the judgment of the Investigator and/or designee, makes the subject a poor candidate for the investigational study – One or more of the limbs has a prior or current diagnosis of PAD, or is reasonably suspected of having a diagnosis of PAD – Subject does not have a suitable finger to attach the FlowMet-R probe – Subject does not have a suitable 1st or 2nd digit to attach the FlowMet-R probe – Subject has undergone revascularization within the last 90 days
Study Procedures and Assessments	**Primary Cohort:** 160 control limbs (Healthy Cohort) will be measured according to Event Schedule C, 240 limbs with PAD, including a minimum subset of 54 limbs with claudication and 100 limbs with CLI, will be measured according to Event Schedule A. PAD patients will be measured at three and six month follow-up (as measured from the baseline visit), according to Event Schedule A. **Registry:** Will be active according to Event Schedule B until data from at least 25 interventional procedures is reached.

3. Introduction

3.1 Background

It is well established in the literature and in clinical practice that diminished blood flow to the extremities, as a result of peripheral artery disease (PAD) or otherwise, may impair wound healing and overall tissue viability [1-5]. PAD is labeled a "large personal, social, and economic burden in the United States" by the American Heart Association and American College of Cardiology. PAD is estimated to affect 8-10 million in the US alone, while having a significant mortality rate (30% mortality in 5 years) [6, 7]. Over $5B is spent annually treating peripheral vascular patients, the majority of which results from late diagnoses, ineffective interventions, and resulting lower limb amputations [8].

One end-stage manifestation of PAD is critical limb ischemia (CLI) [9, 10]. Generally, CLI is defined as: "any patient with chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease" [9]. Early detection and treatment has the potential to keep PAD from reaching the point of CLI. However, traditional methodologies for quantifying extremity blood flow have limitations that prevent widespread clinical adoption. For example, laser Doppler has been used to assess cutaneous blood flow, but measurements are limited to a penetration depth of <1 mm, precluding measurement of the complete microvascular system [11]. Plethysmography can be used to measure relative changes in digital blood volume, but is unable to quantitatively measure perfusion. Doppler ultrasound can be used to quantify flow velocity in the major peripheral arteries, but is unable to measure perfusion rates in the microvasculature. Additionally, the time and cost required for widespread application of ultrasound imaging across large patient populations is restrictive. Transcutaneous oxygen tension has been correlated to CLI severity, but data quality is highly user and position dependent and data acquisition is time-consuming [12, 13]. Angiography is the gold standard for anatomical visualization of blood vessel structure and stenosis. However, angiographic information does not provide simple and functional metrics of blood flow, especially in the case of multiple stenoses. As such, the relationship between extremity blood flow and PAD/CLI cannot be elucidated without a more appropriate methodology for quantifying peripheral perfusion.

The ankle brachial index (ABI) is perhaps the most widely used screening technique to diagnose PAD. While the ABI is relatively simple to perform, it is a ratio of systolic blood pressures rather than a direct measurement of blood flow, and, despite its widespread usage, is only a proxy of direct perfusion measurements. Generally, a cutoff of ABI<0.91 is used to predict the presence of PAD, and a cutoff of ABI<0.4 is used to predict the presence of severe PAD indicating CLI [14]. In diagnosing >50% stenosis of lower limb arteries, researchers have found the ABI to have relatively high specificity, ranging from approximately 83%-99%, but highly variable sensitivity, ranging approximately 15%-79% [15]. In patients with partially non-compressible arteries, ABI values may be inflated and appear normal, despite the presence of significant disease. When the ABI is in a normal range but PAD is suspected, a postexercise ABI may be used to provide additional confirmation. A drop in >30mmHg ankle pressure or

ABI of >20% after exercise indicates the presence of significant disease [16]. The postexercise ABI may be performed with a treadmill test or repeated heel-raises [16].

While ABI has a relatively good sensitivity and specificity for claudication, recent data has shown that over 30% of patients with documented CLI have a normal ABI or ABI consistent with non-compressible blood vessels [17-19]. Therefore, in patients with wounds and/or gangrene, TBI is often used to assist in confirmation [20].

Color duplex ultrasound (CDU/CDI) imaging is often considered the gold standard when assessing arterial stenosis in a vascular laboratory, and good agreement has been shown between duplex and digital subtraction angiography (DSA) [21]. Generally, when assessing the performance of other diagnostic metrics such as ABI, Duplex ultrasound may be used as a gold standard to determine presence of >50% stenosis, indicating significant PAD [15, 22].

While the noninvasive technologies mentioned above are considered standard of care in vascular medicine, there remains a lack of simple and continuous methods to assess PAD severity. A portable technology capable of quantifying disease severity simply and in real time could significantly ameliorate diagnosis, surgical treatment, and follow up care.

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This study has many clinical implications. FlowMet-R is the first noninvasive technology to provide accurate and continuous quantification of microvascular perfusion. Hence, this technology may provide improved diagnostic and/or prognostic capabilities during procedures and in outpatient settings. The current study will set the foundation for future indications of FlowMet-R technology in vascular care.

3.2 Purpose

The purpose of the investigation is to assess the efficacy of the FlowMet-R device in diagnosing PAD and CLI in patients scheduled for peripheral vascular examination. The results of the assessment of the FlowMet-R device will be compared to gold standard diagnostics including ABI, TBI, and Doppler Ultrasound.

4. Objectives and/or Endpoints

4.1 Objectives

4.1.1 Primary Objective(s)

The primary objective of this study is to determine the efficacy of FlowMet-R measurements in diagnosing PAD and CLI. To accomplish this objective, FlowMet-R data (comprised of blood flow

measurements and/or feature analysis of the blood flow waveform) will be used to create a predictive model of PAD severity. This model will then be used to generate diagnostic ROC curves for PAD and, independently, CLI, at multiple time points. The following endpoints will be used to assess fulfillment of this objective:

4.1.1.1 Primary Endpoints

Employ a predictive model based upon FlowMet-R data to generate ROC curves for the diagnosis of PAD and, independently, CLI. ROC curves will be generated at the initial, three month, and six month time points, and will be used to compute the peak sensitivity, peak specificity, and area under the curve (AUC).

4.1.1.1.1 Definitions of PAD and CLI

- Two types of positive diagnosis of PAD will be explored according to published literature: (1) ABI≤0.9 or ABI>1.4 and secondary verification of TBI≤0.7 with exhibition of at least mild claudication (Rutherford Category > 0), or (2) ABI≤0.9 or ABI>1.4 and secondary verification of TBI≤0.7 without exhibition of symptoms. In either case, if the patient displays normal ABI but PAD is suspected, then a postexercise ABI will be performed using a 1-minute treadmill test or heel-raises. A postexercise drop of ABI ≥ 20% or pressure drop ≥ 30mmHg will be considered a positive diagnosis [16].
- A positive diagnosis of CLI will be defined by exhibition of chronic rest pain and active wounds, verified by TBI < 0.3.
- Patients that are enrolled in the PAD positive cohort but are not positively diagnosed for PAD using the above definition (either because their disease is improving or they were screened incorrectly) will be considered PAD negative but will not be grouped into the healthy cohort.

4.1.2 Secondary Objective(s)

The secondary objectives seek to discover the relationship between FlowMet-R measurements and several additional metrics important in vascular medicine. First, the capability of FlowMet-R in the prognosis of requiring a vascular intervention or amputation within three and six months following initial visit will be determined. Additionally, the correlation between FlowMet-R measurements and peripheral artery stenosis will be investigated. Finally, the correlation between changes in ABI/TBI/Rutherford Classification and changes in FlowMet-R data between any two time points will be assessed.

4.1.2.1 Secondary Endpoints

- Utilize FlowMet-R data to create a predictive model for the prognosis of vascular intervention within a three and six month timeframe from initial visit.
- Employ the predictive model of PAD severity to generate an ROC curve for diagnosis of significant stenosis (>50%) in the iliac, femoral, popliteal, peroneal, or tibial arteries.
- Conduct a correlation test between the predictive model of PAD severity and greatest percent stenosis in the iliac, femoral, popliteal, peroneal, or tibial arteries.

– Conduct a correlation test between changes in the predictive model of PAD severity and corresponding changes in ABI, TBI, and Rutherford Classification between any two study time points.

5. Study Design

This is a non-randomized, multi-center, longitudinal study of healthy subjects and subjects with PAD who are scheduled for ABI, TBI, and either Duplex ultrasound or Angiographic assessments in a vascular clinic. As detailed in the Event Schedules (Section 9.1), subjects will first be evaluated for study inclusion/exclusion. If the subject meets the inclusion criteria and wishes to enroll in the study, they will be asked to sign an informed consent form (ICF) and considered for enrollment. If the subject meets inclusion criteria and is enrolled, the subject will undergo approximately 3 minutes of FlowMet-R blood flow measurements in addition to their routine standard of care examination.

Subjects enrolled in the PAD cohort will be assessed according to Event Schedule A at approximately 0, 3 months, and 6 months. Subject follow ups must meet the scheduled time window within +/- 30 days. Subjects that require a vascular (re)intervention for PAD-related treatment before the final measurement (6 month follow up) will have pertinent data collected and saved in the study registry. The vascular procedure may change the timing with respect to the amount of months after baseline that the follow up visits occur. In that case, the standard of care follow up visits post intervention will be adhered to, and data will be collected from the follow up visits that correspond most closely to timepoints at 3 and/or 6 months post baseline visit.

Subjects enrolled in the Healthy cohort will be assessed according to Event Schedule C at a single time point. Imaging outside standard of care will not be performed on the healthy subjects, and healthy cohort subjects with normal ABI and TBI values will be assumed not to have significant peripheral arterial stenosis.

A registry will be established to store measurements acquired from patients who are enrolled in this study and who undergo surgical (re)intervention to address PAD-related symptoms. The collection of data during intervention may occur at any time following the initial and up to the final visit (6 month follow-up). Collected information will include, at minimum, a digitized copy of the intraprocedural record log, all timestamped angiographic films collected during the procedure, and continuous FlowMet-R data collected from the digits of the treated limb. This portion of the study is exploratory and considered hypothesis-generating. Therefore, no objectives or endpoints are currently established for data collected in the registry. For any subject undergoing (re)intervention during the course of this study, the treating physician and all associated site personnel will be blinded to the FlowMet-R outputs during the course of the procedure to eliminate any bias or procedural-based determinations on any outputs not validated.

5.1 Duration

The expected study duration is approximately 6-12 months. The duration of individual subject participation will vary based on timing of their enrollment and completion of the final follow-up visit; however, at a minimum, participation of an individual subject will be at least 6 months.

5.2 Rationale

The study will assess the FlowMet-R's ability to provide a simple and continuous method of assessing PAD severity. To achieve the objectives defined in Section 4.1, FlowMet-R measurements will be acquired from the limbs of enrolled patients and the relationship between the FlowMet-R data and positive diagnosis of PAD and CLI will be evaluated at multiple time points (initial measurement, 3 month follow up, and 6 month follow up). Resulting sensitivity, specificity, accuracy, and receiver operating characteristic (ROC) curves will be generated to demonstrate diagnostic capability. FlowMet-R measurements, along with additional pertinent surgical data, will be collected during revascularization procedures from enrolled patients who require surgical intervention. Additionally, changes in FlowMet-R data for enrolled patients at each study time point will be compared to corresponding changes in ankle brachial index (ABI), toe brachial index (TBI), or patient symptoms. Finally, the prognostic capability of FlowMet-R data will be assessed by calculating the sensitivity and specificity of predicting whether surgical (re)intervention will be necessary following initial assessment.

5.2.1 Prior Benchtop and Animal Studies

The FlowMet-R has been validated on the benchtop using an artificial digit coupled with a syringe pump. When the FlowMet-R was used to measure the flow of a blood-simulating fluid through the artificial digit at controlled volumetric flow rates representing the known physiological range, the FlowMet-R output exhibited a linear response with respect to the known volumetric flow rate (R^2=0.999). Additionally, the FlowMet-R has been tested in animal studies on New Zealand white rabbits and Yorkshire pigs. New Zealand white rabbits (n=5) undergoing cyanide poisoning and resuscitation have been monitored using the FlowMet-R for the purpose of assessing peripheral blood flow. Yorkshire pigs (n=3) undergoing anesthesia have been monitored using the FlowMet-R to assess blood flow within various regions of the pig's core and extremities. In both studies, the FlowMet-R was used to detect increased blood flow during periods of known vasodilation and decreased blood flow during periods of known vasoconstriction and periods of measured decreases in cardiac output.

5.2.2 Prior Clinical Studies

The FlowMet-R has been used previously as a non-significant risk device to study peripheral blood flow in five IRB-approved studies without adverse events. The first study (n=37) was a validation study performed at the University of California, Irvine (UCI IRB HS# 2006-4876). The protocol compared blood flow measurements during before, during, and after brachial artery occlusion using both the FlowMet-R and a laser Doppler system (Perimed Periflux). The study demonstrated a significant correlation between FlowMet-R and the laser Doppler systems (all trials showed $R > 0.7$). A second study (n=47)

aimed to correlate the FlowMet-R to the degree of wound in healing in patients with chronic wounds. This study was performed as Good Samaritan Hospital, San Jose CA (GSH FWA# 00006889). A third study (ongoing) at UCI (HS#: 2016-3286) is designed to measure blood flow dynamics in patients under anesthesia. A fourth study at the Vascular and Interventional Specialists of Orange County (VISOC) outpatient clinic in Orange, CA, collected correlative data between FlowMet-R, Rutherford category, ABI, and TBI in 100 patients (WIRB #1177294). A fifth study was conducted at the Cleveland Clinic, with results presented at ACC March 2018. The final two aforementioned studies found that FlowMet-R data could be used to produce a metric which is significantly correlated to TBI and ABI. In totality, these studies suggest that FlowMet-R measurement are correlated to existing standards used to assess vascular functionality and they provide evidence supporting the safety for FlowMet-R. No adverse events have been reported in any study.

5.3 Study Oversight

The FlowMet study will be monitored by the sponsor and a third-party research organization, [redacted] and made available for monitoring, auditing, IRB review and regulatory inspection by providing direct access to study related source data.

Table 1: **Clinical Research Organization**

CRO	Contact Information
[redacted]	[redacted]

6. Product Description

6.1 General

Device trade name: FlowMet-R

The FlowMet-R is a non-invasive, optical device designed to measure the blood circulation or perfusion rate in peripheral tissue such as the fingers and toes. It comprises a control unit with a digital touch screen user interface, and a measurement device (resembling a pulse oximeter) that easily clips onto the patient's finger or toe. An image of the FlowMet-R system can be seen in Figure 1.

Figure 1: FlowMet-R System Comprised of Digit-Worn Probe and Touchscreen Display

The FlowMet-R instrument head is a compact toe clip designed to be portable and simple to operate. The clip consists of three main primary components: a low-power near infrared laser diode, a complementary metal–oxide–semiconductor (CMOS) digital camera sensor, and device housing.

During FlowMet-R operation, light from the laser diode illuminates and diffuses into the tissue. The diffusion of light is governed by the amount of scattering and absorption within the tissue [23-25]. Diffuse light transmits through the medium and onto a camera sensor. This creates a well-defined pattern, called "laser speckle," which is recorded by the camera sensor and used to quantify blood flow in real-time. Image processing techniques are used to convert collected images into a single value representing the average microvascular blood flow within the tissues being measured. These techniques have become ubiquitous within the biomedical optics research literature [26].

The FlowMet-R received 510(k) clearance from the FDA in March, 2019. It has been certified by [redacted], an independent medical device testing and certification agency to be compliant with IEC 60601-1 and IEC 60825-1, which are standards relating to requirements for electrical safety of medical devices and the safety of laser products, respectively. The laser diode power is below the IEC 60825-1 maximum permissible exposure limits for skin, meaning it does not pose a risk to the tissue being measured. The FlowMet-R has been certified to be compliant as Class I laser product, meaning that it can be safely viewed during use without use of any eye protection. Compliance with IEC 60601-1 indicates that the FlowMet-R does not pose an electronic or mechanical risk to the patient or user. Lastly, skin-contacting

materials on the FlowMet-R have been tested by [redacted], an independent testing and certification agency, to be biocompatible via compliance with ISO 10993-5 and ISO 10993-10 (standards relating to biocompatibility of medical devices). These results indicate that the FlowMet-R does not induce harmful cytotoxicity, sensitization, or irritation when in contact with skin.

The FlowMet-R should not be used in an MR environment or in a hyperbaric oxygen chamber. This could result in unexpected behavior and bodily harm. This FlowMet-R is not defibrillation proof per IEC 60601-1 clause 8.5.5. Personnel involved in this study should review the user manual and instructions for use for the FlowMet-R which describes proper use of the FlowMet-R prior to use. There are no other potentially dangerous elements.

6.2 Device Risk

The FlowMet-R is FDA cleared and Medtronic (previously LAS) has determined that the FlowMet-R should be classified as a non-significant risk device. The following table, Table 1, outlines the US Food and Drug Administration's description of a significant risk device as per 21 CFR 812.3(m) and why these qualities do not apply to the FlowMet-R.

Under 21 CFR 812.3(m), a significant risk device means an investigational device that:	Does the FlowMet-R meet this criterion?	Rationale
Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject	No	The FlowMet-R is not intended as an implant. It is used external to the body to measure blood flow using light.
Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject	No	The FlowMet-R will be used to measure extremity blood flow, and does not perform any life-sustaining functions in doing so.
Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject	No	The FlowMet-R will be used to collect extremity blood flow measurements for comparison against existing standard assessments of vascular health. FlowMet-R data will not be used in any way to diagnose, cure, mitigate, treat, or change the treatment of enrolled subjects.
Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject	No	FlowMet-R measurements are performed non-invasively using light and do not present a serious risk to the health, safety, or welfare of enrolled subjects.

Table 1: FDA Non-Significant Risk Designation as per 21 CFR 812.3(m)

6.3 Product Accountability

The FlowMet-R received 510(k) clearance from FDA and product supply will be managed in a manner consistent with other market-released products.

7. Study Site Requirements

7.1 Study Site Activation

Study site activation is managed by [redacted]. During the activation process (prior to subject enrollment), [redacted] will train study site personnel on the clinical investigation plan, relevant standards and regulations, informed consent, and data collection and reporting tools.

Prior to performing study related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- IRB approval of the current version of the clinical investigation plan and informed consent
- Fully executed clinical trial agreement
- Financial Disclosure
- CV of investigators and key members of the investigation study site
- Documentation of delegated tasks
- Documentation of study training

In addition, all participating study site staff must be trained on the current version of the CIP as well as on the applicable study requirements depending on their role and must be delegated by the principal investigator to perform study-related activities.

Each study site will be provided with documentation of study site/investigator readiness; this notification must be received prior to performing study-related activities.

8. Selection of Subjects

8.1 Study Population

Subjects shall be enrolled until the following number of limbs have been measured under Event Schedule A (Section 9.1):

- 160 control limbs (no diagnosed PAD)
- 240 limbs with PAD
- Of the limbs with PAD, a subset >100 limbs with CLI
- Of the limbs with PAD, a subset >54 limbs without CLI

Any patient being seen for diagnosis of suspected PAD may be screened for enrollment in the PAD cohort. For patients undergoing intervention, supplemental data will be taken within a catheterization laboratory. Control data from a healthy cohort will also be gathered. Recruitment of healthy subjects is at the site's discretion. Third party recruitment services such as researchmatch.org may be used.

8.2 Subject Enrollment

First, the patient will be asked if he/she would like to participate in the study. If so, they will undergo the informed consent procedure.

When a subject and the principal investigator or authorized designee, as required, have personally signed and dated the IC, the subject is considered to be enrolled in the study. The date the subject signed the IC must be documented in the subject's medical records.

Subjects will be screened to ensure they meet all of the inclusion and none of the exclusion criteria prior to study enrollment.

8.3 Inclusion Criteria

Candidates for this study must meet ALL of the following inclusion criteria:

PAD Positive Cohort

- Subject meets PAD positive criteria set forth in Section 8.3
- Subject is willing and able to provide an informed consent.
- Subject is willing and able to comply with the study procedures.
- Subject is able to understand the study procedures.
- Subject is scheduled for vascular examination that includes noninvasive assessments as standard of care: ABI, TBI, and either a Duplex ultrasound or Angiogram.

Healthy Cohort

- Subject is willing and able to provide an informed consent.
- Subject is willing and able to comply with the study procedures.
- Subject is able to understand the study procedures.
- Subject has no history of positive PAD diagnosis and is not currently suspected of having PAD.

8.4 Exclusion Criteria

Candidates for this study who meet any of the following criteria at the time of the baseline visit are NOT eligible to be enrolled in this study:

PAD Positive Cohort Exclusion

- Subject is under 40 or unable to consent.
- Subject has any medical condition, which, in the judgment of the Investigator and/or designee, makes the subject a poor candidate for the investigational study.
- Subject is excluded from analysis if no stenosis is found during Doppler but Tibial disease is suspected and Tibial ultrasound is not able to be performed.
- Subject does not have a suitable finger to attach the FlowMet-R probe.
- Subject does not have a suitable 1st or 2nd digit to attach FlowMet-R probe on the limb of interest.
- Subject has undergone revascularization within the last 90 days

- Subject cannot lay safely in a supine position.

Healthy Cohort Exclusion

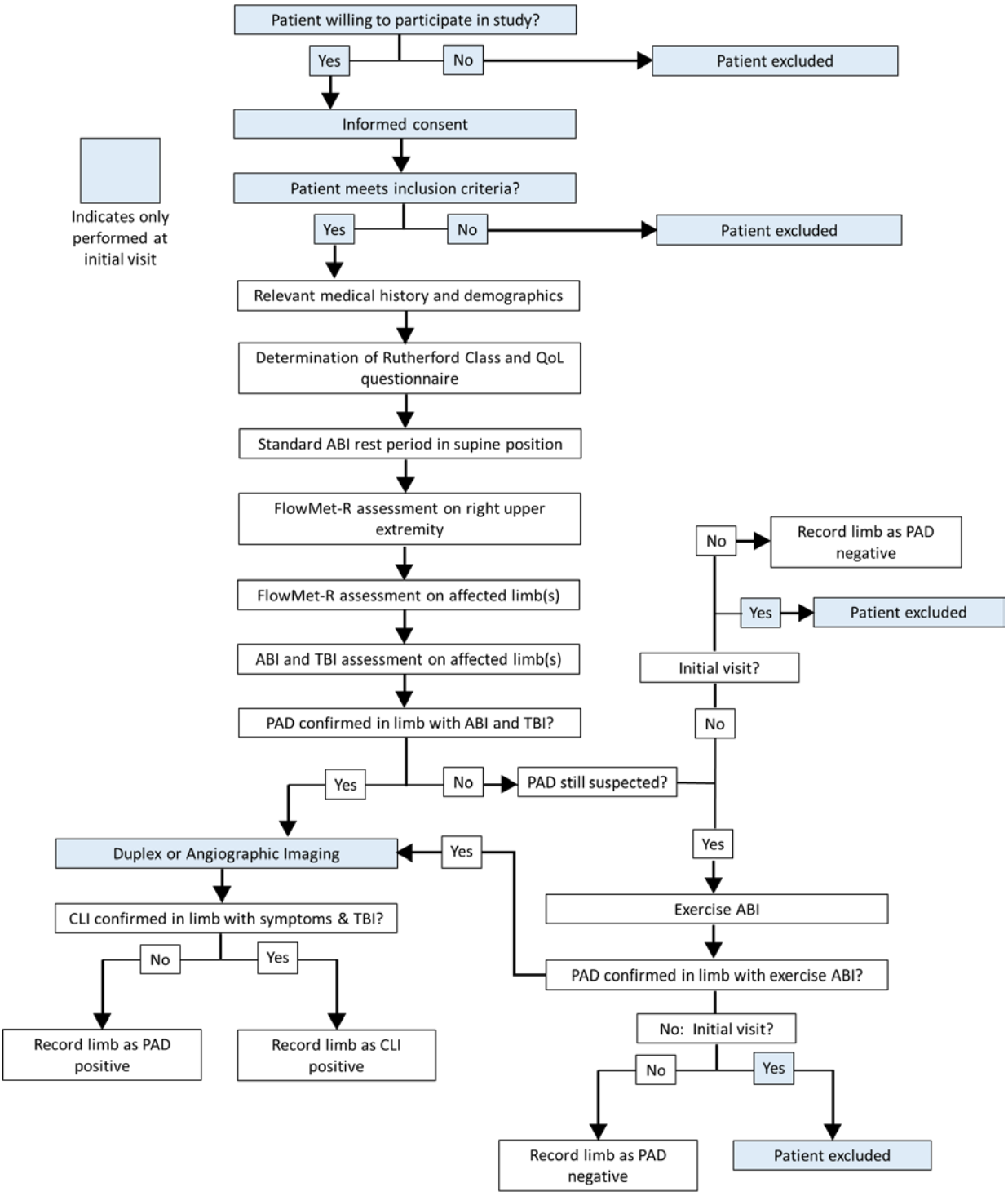
- Subject is under 40 or unable to consent.
- Subject has any medical condition, which, in the judgment of the Investigator and/or designee, makes the subject a poor candidate for the investigational study.
- One or more limbs has a prior or current diagnosis of PAD, or is reasonably suspected of having a diagnosis of PAD.
- Subject does not have a suitable finger to attach the FlowMet-R probe.
- Subject does not have a suitable 1st or 2nd digit to attach FlowMet-R probe.
- Subject has undergone revascularization within the last 90 days

9. Study Procedures

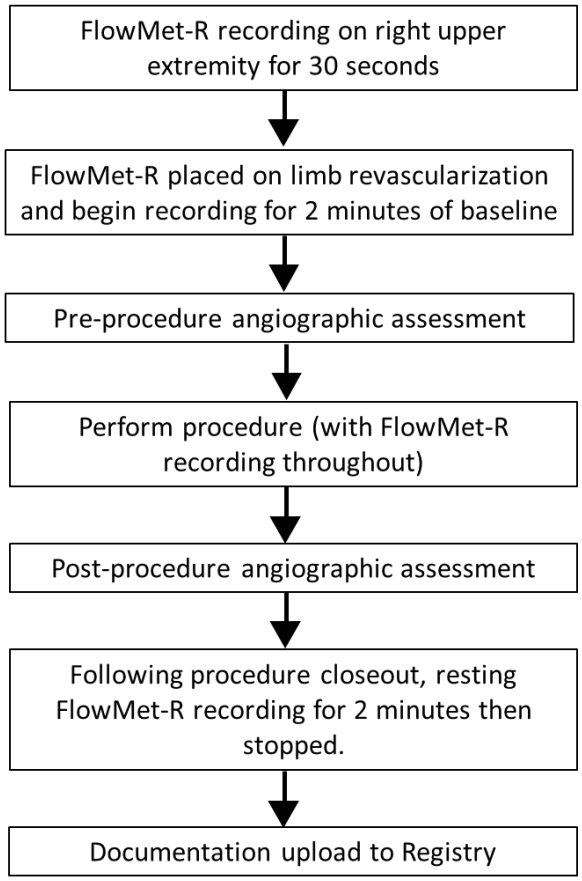
9.1 Schedule of Events

Patients will follow the below event schedules based on their cohort. PAD patients will follow Event Schedule A, Registry patients will follow Event Schedule B, and the Healthy Cohort subjects will follow Event Schedule C.

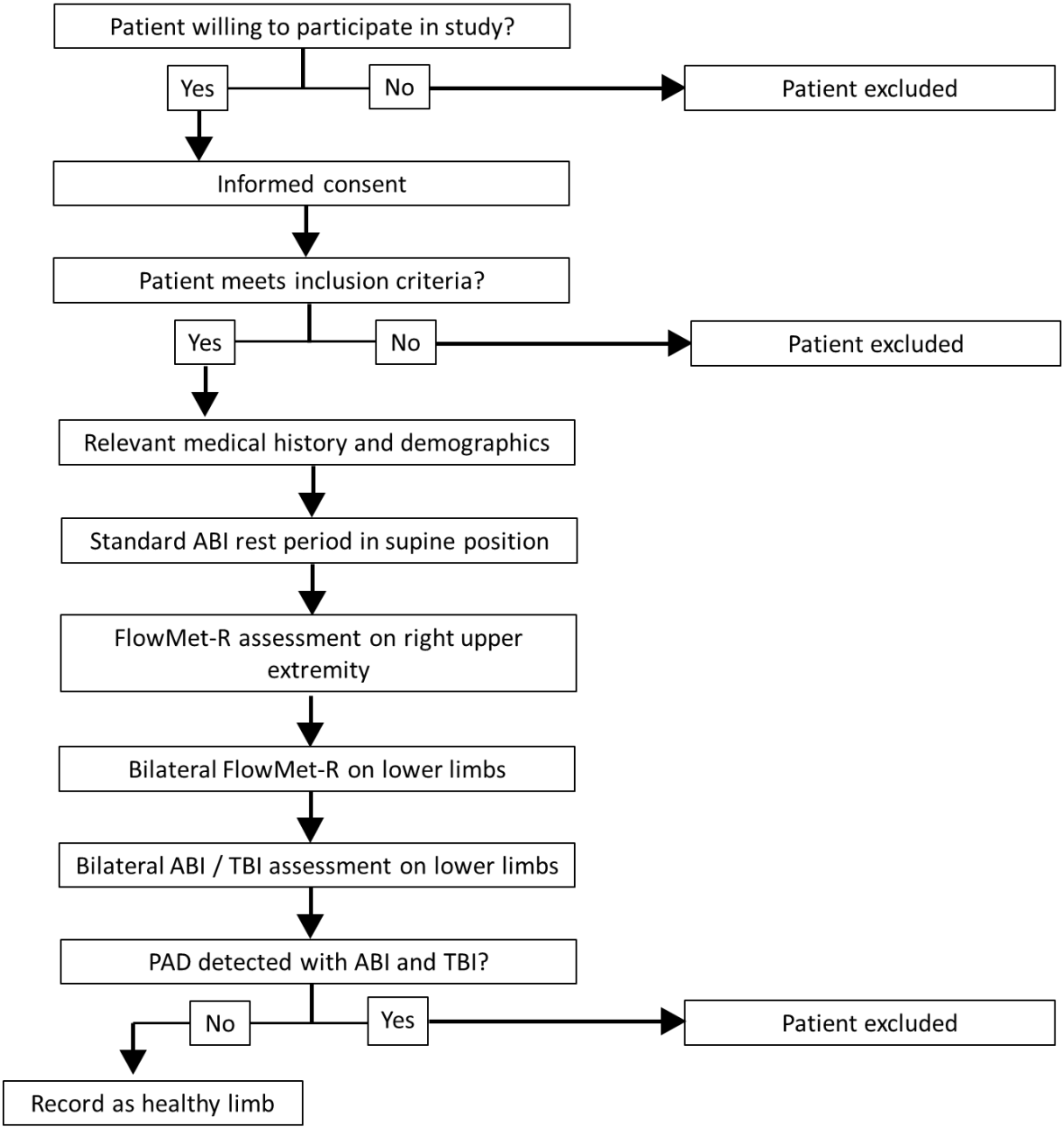
Initial and Follow-Up Visits: Event Schedule A


Patient willing to participate in study?
Yes
No
Patient excluded
Informed consent
Patient meets inclusion criteria?
Yes
No
Patient excluded
Indicates only performed at initial visit
Relevant medical history and demographics
Determination of Rutherford Class and QoL questionnaire
Standard ABI rest period in supine position
FlowMet-R assessment on right upper extremity
FlowMet-R assessment on affected limb(s)
ABI and TBI assessment on affected limb(s)
PAD confirmed in limb with ABI and TBI?
Yes
No
PAD still suspected?
No
Record limb as PAD negative
Yes
Patient excluded
Initial visit?
No
Yes
Duplex or Angiographic Imaging
Yes
CLI confirmed in limb with symptoms & TBI?
No
Yes
Record limb as PAD positive
Record limb as CLI positive
Exercise ABI
PAD confirmed in limb with exercise ABI?
No: Initial visit?
No
Yes
Record limb as PAD negative
Patient excluded

Interventional Procedure: Event Schedule B



Healthy Cohort Single Visit: Event Schedule C



9.2 Data Collection

Data collection requirements are summarized in Table 2 below.

Table 2: Data collection and study procedure requirements at subject visits

Study Procedure	Baseline	Registry Entry (if applicable)	3 month	6 month	Study Exit
Informed Consent	X				
Inclusion/exclusion assessment	X				
Medical History/Demographics	X		X	X	
Rutherford Grade	X		X	X	
QoL Survey	X		X	X	
FlowMet Collection	X		X	X	
FlowMet Collection Intraprocedure		X			
ABI/TBI	X		X	X	
Exit subject					X
AEs	As they occur				
Study deviations	As they occur				

9.3 Scheduled Follow-up Visit Windows

The target dates and windows for each visit are detailed in the table below. Should a subject miss a visit or the visit fall outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits.

Data analyses include follow-up visits regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit, but must be accompanied by a deviation report. Follow-up visit windows are listed in Table 3, and are based on days post-FlowMet-R assessment.

Table 3: Data collection and study procedure requirements at subject visits

Study Follow-up Visit	Window (Calculated days post-FlowMet-R Assessment)		
	Window Start	Target	Window End
Follow-up Visit 1	2 months	3 months	4 months
Follow-up Visit 2	5 months	6 months	7 months

9.4 Subject Consent

Informed consent is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular study. This process includes obtaining an Informed Consent Form that has been approved by the study site's IRB and signed and dated by the subject. A subject may only consent after information has been given and explained to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate.

Prior to enrolling subjects, the informed consent must be approved by the site's IRB. The document must be controlled to ensure it is clear which version was approved by the IRB. Any adaptation of the sample informed consent must be reviewed and approved by Medtronic and the IRB reviewing the application prior to enrolling subjects.

The investigator must notify the subject of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study. If relevant, consent may be requested from subjects to confirm their continued participation.

Prior to initiation of any study-specific procedures, informed consent must be obtained from the subject. The informed consent process must be conducted by the principal investigator or an authorized designee, and the informed consent form must be given to the subject in a language he/she is able to read and understand. The process of informed consent must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other study site personnel. The informed consent process shall not waive or appear to waive subject's legal right. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the informed consent form, to inquire about details of the study, and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the study, the informed consent must be signed and personally dated by the subject and investigator or authorized designee, as required by the informed consent, and ensured by the principal investigator or his/her authorized designee.

A copy of the informed consent, signed and dated as required by law, must be provided to the subject.

If the informed consent is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures.

In the event that the subject cannot read and/or write, the informed consent process shall be obtained through a supervised oral process. An independent and impartial witness must be present during this process. This informed consent and any other information must be read aloud to the prospective subject. Whenever possible, the subject shall sign and personally date the informed consent form. The witness signs and personally dates the informed consent attesting that the information was accurately explained and that informed consent was freely given.

The original signed informed consent must be filed in the hospital/clinical chart and/or with the subject's study documents. The informed consent must be available for monitoring and auditing.

9.5 Baseline Visit

9.5.1 Relevant Medical History and Demographics

The clinician will document demographics and medical history on the associated Case Report Forms and enter them into the Electronic Data Capture (EDC) system.

For patients that are seen for a vascular (re)intervention and are part of the registry portion of the study, standard information about the patient's scheduled intervention, treatment plan, and follow up schedule will be contained in the record log and uploaded as a digital copy.

9.5.2 QoL Assessment

Quality of Life (QoL) assessments are an important reporting standard for PAD patients. The VascuQoL is a questionnaire that has been used frequently by clinical studies in the past in evaluating QoL in CLI and Claudication patients [28]. Here, we choose to use the abbreviated VascuQoL-6, a 6 item survey that has been shown to be as effective as the standard VascuQoL, but with reduced time burden on patients and clinicians [29].

9.5.3 Rutherford Classification / Visual Assessment

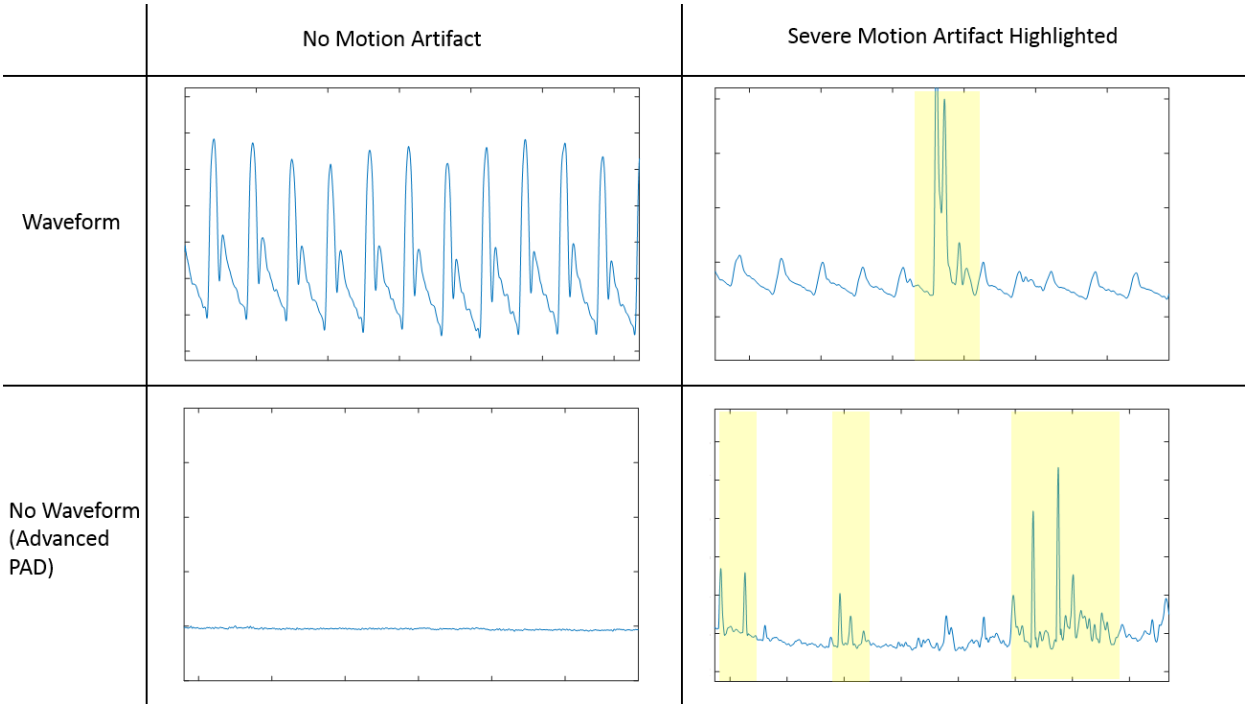
The Rutherford scoring system is commonly used in vascular assessment of PAD patients. Grade and category will both be recorded for enrolled patients on the CRF. The clinician will also note visual inspection of limbs for evidence of ulcers or wounds. If present, wound grade and foot infection grade will be noted as well as wound healing trajectory.

9.6 FlowMet-R Assessment

FlowMet-R measurements will be taken before noninvasive testing as detailed in Event Schedule A. Clinical personnel must be trained on use of the FlowMet-R device prior to measurement. Details of the measurement acquisition procedure are as follows:

- A patient rest period shall be performed in accordance with standard ABI collection before FlowMet-R or ABI measurement. Extremity blood flow measurements will be performed using the FlowMet-R device in the following order: index finger of the upper right hand (if the index finger is unavailable another finger may be used), and on the great toe (if the great toe is not available the 2nd toe may be used, and this will be noted in the CRF) of the limbs being measured. If measuring bilaterally, the right side will be performed first.
- Once the probe is placed on the digit, flow will be allowed to equilibrate for approximately 30 seconds before checking signal quality to allow transient changes in perfusion to diminish. Signal quality will be confirmed by observing the presence of a pulse waveform (if one is expected), or by the stability of the flatline (in the case of complete occlusion). The clinician will also ensure that an appropriate amount of light is detected by the FlowMet-R device. The following light intensity values are acceptable: maximum intensity greater than 30 but less than 255 and average intensity greater than 25 but less than 200. The FlowMet-R device will indicate to the clinician if the intensity is outside of proper bounds by displaying a warning. The clinician should then adjust the probe until the warning disappears.
- The patient shall be instructed not to move, laugh, talk, etc. during the measurement. These actions can cause erroneous FlowMet-R measurements due to movement artifact. If this occurs, the measurement will need to be repeated and this should be noted in the CRF.
- Following the 30 second equilibration period, the clinician will then record FlowMet-R blood flow data for approximately 30 seconds using the data acquisition software, which will save the data on the local hard drive. Once data collection is complete, the clinician will note the “flow value” and waveform fidelity displayed in the software on the CRF.
- A post-hoc data quality check must be performed before taking the next flow measurement. Data fidelity will be assessed by observing the recorded waveform using the analysis tab of the software. The flow waveform should appear periodic without large unexpected spikes (indicating motion artifact) or sections that are missing (indicating over- or under- exposure). See Figure 3 (top) for examples of high quality flow waveform data and compromised data. In cases of advanced disease, the waveform may be severely dampened or not be present at all. In cases where advanced disease has occluded blood flow and a waveform is not expected, the user will check the flow measurement to ensure the flow graph is relatively flat and there are no major motion artifacts in the flow recording. See Figure 3 (bottom) for examples of high quality and compromised data from patients with advanced disease.
- If the post-hoc data quality check reveals poor quality or missing data, steps 2-5 must be repeated until acceptable data has been recorded. This may require a repositioning of the probe. If 5 or more repeated attempts are made and poor quality data persists, the clinician will choose the optimal record to the best of their knowledge.

Figure 3: Example illustrations of high fidelity flow measurements (left column) compared with flow measurements that are corrupted by artifact (right column).



9.6.1 Product Equipment

9.6.1.1 FlowMet-R

The FlowMet-R is a non-invasive optical device that measures real time blood flow/perfusion rate in the extremities using the principles of laser speckle imaging (LSI). To perform LSI, tissue is illuminated with coherent laser light, which scatters off moving red blood cells and produces a speckle pattern. The pattern is recorded on an image sensor and the characteristics can be used to measure blood flow/perfusion, as demonstrated in prior literature [26].

During use, the FlowMet-R probe is affixed onto the toes using a spring-loaded clip, with the light source (laser diode) and image sensor (digital camera) on opposite sides. The image sensor and readout circuitry are custom designed for a compact profile and adequate spatial sampling of the speckle pattern [27]. Molded, biocompatible silicone pads are used within the FlowMet-R probe in locations where the device contacts skin. Data acquisition, processing, display, and user interaction is performed using custom software run on a computer with Windows 10 operating system. Between uses, the skin-contacting silicone pads and probe housing can be sanitized using alcohol wipes or germicidal wipes, such as PSI Inc. Sani-Cloths, which are commonly used in hospitals and which are bactericidal, tuberculocidal, and virucidal. The FlowMet-R has been used in NSR-designated IRB approved studies on

more than 100 patients without adverse events. The FlowMet-R was 510(k) cleared by the FDA in early March, 2019.

If the FlowMet-R system malfunctions and/or needs to be serviced, this will be reported on the EDC and to Medtronic. Medtronic will provide technical assistance within 48 hours. If the system requires repair or replacement, Medtronic will provide a new unit to the site within 5 business days.

9.6.1.2 Automatic ABI System

Medtronic will provide an automated PAD system, the Flolab (Parks Medical Electronics, Inc., Aloha, OR) which will be provided to each site by Medtronic and used to perform ABI and TBI measurements. An automated device can improve measurement consistency between sites and help reduce inter-operator differences. The system includes a 4 Piece set of standard 8½"-14" (22 cm-36 cm) cuffs, a PPG monitor, and a control unit, which is used to automatically perform bilateral ABI and TBI measurements. Measurements results will be printed out and included in the CRF. If the automated system cannot be used or is unavailable, manual ABI and TBI measurements will be performed. Clinical personnel must be trained on use of the Flolab device prior to taking ABI and TBI measurements with the system.

9.7 Standard Noninvasive Vascular Assessments

Noninvasive testing and Duplex imaging results will be evaluated on the same leg(s) used to collect FlowMet-R data with the patients lying supine. The results will be recorded on the CRF. If color duplex imaging is not scheduled as standard of care, angiographic images taken within 30 days prior to the noninvasive measurements may be used for calculation of stenosis percentage.

9.7.1 Toe brachial index (TBI)

A patient rest period shall be performed in accordance with standard ABI/TBI collection before FlowMet-R or ABI/TBI measurement. Brachial pressures and toe pressures on both lower limbs (if applicable) will be measured according to the 2016 guidelines provided by the ACC/AHA using an automated TBI system. A PPG device will be used to detect the toe waveform. Measurement results will be recorded on the CRF.

9.7.2 Ankle brachial index (ABI)

A patient rest period shall be performed in accordance with standard ABI/TBI collection before FlowMet-R or ABI/TBI measurement. Brachial pressures and ankle pressures on both lower limbs (if applicable) will be measured according the 2016 guidelines provided by the ACC/AHA using an automated sphygmomanometer-based system. Measurement results will be recorded on the CRF.

9.7.3 Postexercise ankle brachial index (ABI)

If an enrolled patient's ABI and TBI measurements classify that patient as not having PAD/CLI as per the definitions in Section 8.4, but it is suspected that the patient may have PAD based upon medical history or clinical symptoms, a postexercise ABI measurement will be performed. For such patients, guidelines

provided by the ACC/AHA will be followed. A treadmill or heel-raise test will be considered an acceptable challenge for measurement of postexercise ABI.

9.7.4 Duplex ultrasound

Color duplex ultrasound measurements shall be used to determine stenosis percentage and location, either during the visit itself or within 30 days prior of the patient visit. Duplex shall be acquired from all limbs enrolled in the study with PAD/CLI as defined via the definitions in Section 8.4. If duplex ultrasound is not available, X-ray angiography will be considered a suitable alternative for calculation of stenosis and location. Color duplex ultrasound imaging will be performed in a similar fashion as the study by Lewis, et al. [30]. First, the distal common femoral artery (CFA) will be imaged and the Doppler waveform (DW) assessed visually for any loss of triphasic flow due to significant iliac disease. If the DW shows indications of this, then the iliac arteries will be assessed for the presence of atherosclerotic disease. The scan will continue distally from the CFA assessing the superficial femoral artery (SFA), popliteal, anterior tibial, posterior tibial, and peroneal arteries in the longitudinal plane. The extent and severity of any arterial disease are assessed by measuring the peak systolic velocity (PSV) from the DW just proximal to and distal through the stenosis. For each measured artery, if perceptible stenosis exists, the location of maximum stenosis will be identified and PSV values distal and proximal to the arterial stenosis will be noted on the CRF. The shape of the waveform (i.e. monophasic, biphasic, or triphasic) measured distal to the stenosis shall also be noted. If no stenosis is noted, this will indicated on the CRF.

9.7.5 X-Ray Angiography

Peripheral angiography may be used as an alternative to duplex ultrasound in the assessment of arterial stenosis percentage and location, and may be performed during the visit itself or within 30 days prior. Angiography is an imaging technique to diagnose narrowed or blocked peripheral arteries, the hallmark of PAD. Angiograms may or may not include dye for improving image contrast. Angiograms have been used for decades and are considered the gold standard for evaluating vascular disease. Advanced techniques, such as the computed tomographic angiogram (CTA), and digital subtraction angiography (DSA) have gained popularity in recent years and have shown reliable sensitivity and specificity for differentiating extend of disease [31].

9.8 Intraprocedural Data Collection

Patients enrolled in the study who undergo revascularization surgery to address PAD/CLI will have pertinent data collected immediately before, during, and immediately after the surgical procedure. The schedule of events is summarized in Event Schedule B above (section 9.1). The following steps shall be followed:

- Prior to the start of the procedure, the FlowMet-R probe will be attached to the upper extremity for a 30-second recording. Next, the probe will be moved to the great toe of the limb being treated. If this digit is not usable, another digit may be used.
- Once the probe is placed on the digit, flow will be allowed to equilibrate for 30 seconds before checking signal quality to allow transient changes in perfusion to diminish. Signal quality will be

confirmed by observing the presence of a pulse waveform (if one is expected), or by the stability of the flatline (in the case of complete occlusion). The clinician will also ensure that an appropriate amount of light is detected by the FlowMet-R device. The following light intensity values are acceptable: maximum intensity greater than 30 but less than 255 and average intensity greater than 25 but less than 200. The FlowMet-R device will indicate to the clinician if the intensity is outside of proper bounds by displaying a warning. The clinician should then adjust the probe until the warning disappears. After proper placement and collection of the FlowMet-R and sensor have been confirmed, the physician shall be blinded to all outputs during and after the course of the intervention.

- Movement of FlowMet-R probe should be minimized during the procedure to prevent motion artifact and measurement errors.
- If the FlowMet-R probe is accidently removed during the procedure or if a data quality warning is displayed by the FlowMet-R software (i.e. too much or too little light is being detected), the probe shall be replaced or reseated on the digit it was originally placed on (if possible). If this is not possible, a different digit may be used and this change shall be noted.
- The digit being measured and patient ID should be entered into the Patient Data section of the FlowMet-R software.
- FlowMet-R data saving shall be initiated prior to state of surgery. Therapies and notable events for each procedure, including timing, shall be recorded.
- The surgical procedure shall take place as per the standard of care.
- At the end of the procedure, FlowMet-R data saving shall be ceased.
- FlowMet-R data, along with angiographic films, and other pertinent information related to the surgical procedure such as patient symptoms and visual assessment shall be uploaded to the registry EDC.

9.9 Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the clinical investigation plan or clinical trial agreement.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness). Any deviation from this protocol will be noted and described in the EDC system under the deviations from protocol section.

9.10 Subject Exit, Withdrawal or Discontinuation

The study exit form should be completed at the time a subject is exited from the study. A subject will be considered to have exited from the study for any of the following reasons.

- Subject completes follow-ups required by the investigational plan
- Subject dies

- Subject requests to be withdrawn
- Physician requests that patient be withdrawn to protect the welfare of the patient
- Subject is lost to follow-up

A subject may elect to withdraw from the study at any time. The subject should notify the investigator. The investigator and research staff should encourage all subjects to return for required follow-up visits. Every attempt must be made to ensure all subjects complete the follow-up schedule. For subjects who fail to appear for a scheduled study visit, the site must contact the subject in a timely manner to reschedule the visit and associated required evaluations within the subject's window, if possible.

10. Risks and Benefits

10.1 Potential Risks

The FlowMet-R is FDA cleared and Medtronic (previously LAS)has determined that the FlowMet-R should be classified as a non-significant risk device. There are no incremental risks introduced to the subject as a result of participation in this study.

10.2 Risk Minimization

The potential risks associated with the FlowMet-R have been successfully mitigated. Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the CIP.

Prior benchtop, animal, and clinical studies have been performed previously.

The FlowMet-R has been validated on the benchtop using an artificial digit coupled with a syringe pump. When the FlowMet-R was used to measure the flow of a blood-simulating fluid through the artificial digit at controlled volumetric flow rates representing the known physiological range, the FlowMet-R output exhibited a linear response with respect to the known volumetric flow rate (R2=0.999). Additionally, the FlowMet-R has been tested in animal studies on New Zealand white rabbits and Yorkshire pigs. New Zealand white rabbits (n=5) undergoing cyanide poisoning and resuscitation have been monitored using the FlowMet-R for the purpose of assessing peripheral blood flow. Yorkshire pigs (n=3) undergoing anesthesia have been monitored using the FlowMet-R to assess blood flow within various regions of the pig's core and extremities. In both studies, the FlowMet-R was used to detect increased blood flow during periods of known vasodilation and decreased blood flow during periods of known vasoconstriction and periods of measured decreases in cardiac output.

The FlowMet-R has been used previously as a non-significant risk device to study peripheral blood flow in five IRB-approved studies without adverse events The first study (n=37) was a validation study performed at the University of California, Irvine (UCI IRB HS# 2006-4876). The protocol compared blood flow measurements during before, during, and after brachial artery occlusion using both the FlowMet-R and a laser Doppler system (Perimed Periflux). The study demonstrated a significant correlation between FlowMet-R and the laser Doppler systems (all trials showed R > 0.7). A second study (n=47) aimed to correlate the FlowMet-R to the degree of wound in healing in patients with chronic wounds. This study was performed as Good Samaritan Hospital, San Jose CA (GSH FWA# 00006889). A third study (ongoing) at UCI (HS#: 2016-3286) is designed to measure blood flow dynamics in patients under anesthesia. A fourth study at the Vascular and Interventional Specialists of Orange County (VISOC)

outpatient clinic in Orange, CA, collected correlative data between FlowMet-R, Rutherford category, ABI, and TBI in 100 patients (WIRB #1177294). A fifth study was conducted at the Cleveland Clinic, with results presented at ACC March 2018. The final two aforementioned studies found that FlowMet-R data could be used to produce a metric which is significantly correlated to TBI and ABI. In totality, these studies suggest that FlowMet-R measurement are correlated to existing standards used to assess vascular functionality and they provide evidence supporting the safety for FlowMet-R. No adverse events have been reported in any study.

10.3 Potential Benefits

There are no anticipated benefits from participation in this study. The information gained from this study could result in improved management and diagnosis of PAD and CLI.

10.4 Risk-Benefit Rationale

The FlowMet-R is FDA cleared and has been classified as a non-significant risk device.

11. Adverse Events and Device Deficiencies

11.1 Adverse Events

Investigators shall submit a report of any device-related or suspected device-related adverse or serious adverse event to the sponsor and IRB as soon as possible, but in no event later than 5 business days after the investigator first learns of the event (§ 812.150(a)(1)). These reports shall be uploaded to the EDC system and will only include adverse events that could reasonably be associated with use of the FlowMet device. All Adverse Events reported to the Sponsor during the study will be reviewed and adequately reported to comply with applicable regulations (ISO 14155:

and vigilance requirements. All adverse events will be classified according, at a minimum, to ISO 14155: . Medtronicwill also determine whether a reported Adverse Event is anticipated or unanticipated. Investigators will be asked to classify whether an adverse event is considered serious or non-serious and whether it is considered device related. If an event is determined to be Serious and device related, investigators will be asked to make a determination as to whether or not the study can remain an NSR study. If needed, this determination will be submitted to the IRB. Potential complications are listed in section 6.2. Unexpected complications are also possible, as any electronic device carries some medical risk. Potential complications include slight discomfort due to warming of the interrogated tissue during normal function of the internal components (approximately <1% probability).

Potential complications include slight discomfort due to warming of the interrogated tissue during normal function of the internal components (approximately <1% probability).

12. Statistical Design and Methods

12.1 General Aspects of Analysis

12.1.1 Sample Size

The rate of PAD and CLI within the population seen at a typical vascular clinic is estimated from prior investigation (i.e WIRB #1177294). In this previous study, 100 limbs were assessed using the ABI and graded using the Rutherford classification scheme. PAD (diagnosed via ABI score of <0.9) was present in 63% of limbs. CLI (estimated as having a Rutherford category of ≥4) occurred in 15% of limbs. FlowMet-R data was also collected from the above limbs, and the data analysis techniques used in the data analysis section below were applied to build a diagnostic model for PAD and CLI. ROC curves were then generated for the diagnosis of both Claudication and CLI. The resulting area under the curve (AUC) for these ROC curves was 0.67 and 0.80, respectively. However, the Claudicant group AUC had a tighter confidence interval due to larger sample size (84 vs. 22).

Using a conservative estimation that the AUC for distinguishing PAD groups from healthy controls remains within +/- 0.05 of the Claudicant group, and +/- 0.2 of the CLI group, an estimate for the necessary sampling size can be determined. A standard type I error rate (α) of 0.05 and power of 0.8 is desired, thus the following approximate sample size was calculated for statistically significant results [32, 33]: 160 control limbs and 240 limbs with PAD, of which at least 54 limbs with Claudication and at least 100 limbs with CLI. Limbs with CLI may be included as a subset of limbs with PAD. A minimum of 250 patients (400 limbs) and maximum of 400 patients will be enrolled in the study.

12.1.2 FlowMet-R data analysis and diagnostic model

FlowMet-R data is comprised of continuous blood flow data recorded over 30 seconds. Over this time, a pulsatile blood flow waveform may be present due to the subject's cardiac cycle, provided that digital blood flow is sufficient to generate such a signal. Thus, a combination of the flow amplitude and one or more features of the waveform may be used as inputs to train the predictive model.

The target outcome variable for training the model shall be a continuous metric of PAD severity, analogous to the ABI or TBI. The training will be performed as a regression using iterative algorithms ubiquitous in machine learning.

The predicted outputs from the regression model will be used to generate an ROC curve by classifying a binary diagnostic (i.e. PAD true/false, CLI true/false), or prognostic (i.e. vascular intervention likely within 6 months (true/false)). The classification algorithm which results in the highest diagnostic area under the curve for PAD and CLI shall be chosen to compute final sensitivity and specificity.

A k-fold cross validation scheme will be implemented to gauge model generalization. k-fold cross validation is a statistical sampling method that can be used to train and objectively validate the above

classification algorithms [34]. Using this scheme, only a subset of the total body of collected data is used to train the model, which is then applied to the remaining data withheld from training prospectively. During this validation stage, the performance and generalizability of the model can be assessed. Cross validation allows more objective selection of the optimal algorithm because performance assessment is based upon applying the model to a data set which it is naïve to (i.e. a prospective application of the model).

12.1.3 Analysis of Stenosis

For each artery measured using duplex ultrasound or arterial angiography, the ratio of the PSV distal to the most prominent stenosis to the PCV proximal to the stenosis will be computed (if applicable). The percent stenosis in such arteries will be computed two ways: (1) Percent stenosis = PSVdistal/PSVproximal, or (2) using the diameter reduction value from Table 3, reprinted from [35].

	Diameter reduction	Waveform	Special broadcasting	PSV distal/PSV proximal
Normal	0	Triphasic	Absent	+++ No change
Mild	1%–19%	Triphasic	Present	<2:1
Moderate	20%–49%	Biphasic	Present	<2:1
Severe	50%–99%	Monophasic	Present	>2:1*

PSV, Peak systolic velocity.
* > 4:1 suggests >75% stenosis, >7:1 suggests > 90% stenosis.

Table 3: Criteria for determining arterial stenosis using peak systolic velocity (PSV) measurements.

Classification of the percent stenosis or presence of greater than 50% stenosis for each limb (used to generate corresponding ROC curve or correlation coefficient) may be determined by either considering a single artery of interest or by considering the artery in each limb with the greatest percent stenosis.

13. Ethics

13.1 Statement(s) of Compliance

This study will be conducted in compliance with Good Clinical Practice. GCP includes review and approval by an independent IRB before initiating a study, continuing review of an ongoing study by and IRB, and obtaining and documenting the freely given informed consent of a subject before initiating the study.

The FlowMet-R study is compliant with ISO 14155.This includes the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigator. In accordance with ISO 14155, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator or other parties participating in or contributing to the clinical investigation.

The principles of the Declaration of Helsinki have been implemented throughout the informed consent process, IRB approval, and study training.

In addition to the regulatory requirements outlined above, the study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the United States, where the study is being conducted. These include, but are not limited to:

- 21 CFR Part 11: Electronic Records, Electronic Signatures
- 21 CFR Part 50: Protection of Human Subjects
- 21 CFR Part 54: Financial Disclosure by Clinical Investigators
- 21 CFR Part 56: IRB
- Principles of the Declaration of Helsinki

14. Study Administration

14.1 Monitoring

The FlowMet-R study will be monitored by the sponsor and a third-party research organization, [redacted], and made available for monitoring, auditing, IRB review and regulator inspection by providing direct access to study related source data. Site monitors will visit the site periodically to ensure adherence to the protocol.

14.2 Data Management

An EDC system will be created that contains the case report forms (CRF) to be filled out for each enrolled subject. The sites may optionally use a paper-based form for collecting key data from the patient during the visit, then upload the results to the EDC post-visit.

All records and other information about subjects participating in this study will be treated as confidential. Procedures in the CIP require source documentation. Source documentation will be maintained at the study site. Source documents, which may include worksheets and subject medical records, , must be created and maintained by the investigational study site team.
The investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical investigation. The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing.

14.3 Direct Access to Source Data/Documents

When applicable, the monitors, auditors, the IRB, the Office of Human Subjects Protection (OHRP) of the Department of Health and Human Services as well as the Food and Drug Administration (FDA) will be granted direct access to medical records for verification of the research procedures and data.

14.4 Confidentiality

The study will be conducted in a manner consistent with the federal Health Insurance Portability and Accountability Act (HIPAA). Only non-identifiable health information will be collected and stored in the EDC database. The research staff at individual sites may use and share information to ensure research meets legal, institutional, or accreditation requirements. If the research team uncovers abuse, neglect, or reportable diseases, this information may be disclosed to appropriate authorities. As part of the study, the PI, study team, and others may disclose non-identifiable protected health information to the following:

- The commercial sponsor and/or their representative Medtronic Inc.
- Contract Research Organization (whose job is to help organizations fulfill their responsibilities in the research and development process): [redacted]
- The United States Food and Drug Administration
- The United States Department of Health and Human Services and the Office of Human Research Protection (OHRP).

In all disclosures outside of individual study sites, no subject shall be identified by name, social security number, address, telephone number, or any other direct personal identifier unless disclosure of the direct identifier is required by law. OHRP and FDA are authorized to remove information with identifiers if necessary to complete their task.

14.5 Liability

14.6 Liability provisions are expressed in each site clinical trial agreement. CIP Amendments

- Any revisions or amendments to the CIP or IC document, along with a statement of justification for the changes, will be submitted to all affected IRBs. All amendments to the CIP shall be agreed upon between Medtronic and the principal investigator(s), or the coordinating investigator. Approval by IRB must be obtained prior to implementing a CIP revision at the study site.

14.7 Record Retention

The investigator will maintain complete and accurate study records in an encrypted file located exclusively at the clinic for 2 years following study closure. The investigator should take measures to prevent accidental or premature destruction of documents. Should the investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to Medtronic.

Medtronic will retain the study records according to Medtronic corporate policy and record retention schedule.

14.8 Suspension or Early Termination

14.8.1 Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a study that occurs when Medtronic requirements have been satisfied per the CIP. Ongoing IRB oversight is required until the overall study closure process is complete.

14.8.2 Early Termination or Suspension

Early Termination is the closure of a study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single study site.

Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single study site.

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16. Appendices

Not Applicable

17. Version History

Version	Summary of changes	Justification of changes	Identification of the affected study documents	Author(s)/Title
3.1	**MAJOR CHANGES**			
	Migration to Medtronic Template	Acquisition of LAS by MDT complete	Informed Consent Form	[redacted]
	Changed FlowMet assessment procedure to implement the standard of care rest period for ABI/TBI instead of FlowMet-specific 5 minute rest period. The same rest period may be applied for FlowMet and ABI/TBI measurements.	Changed to ensure sites can follow their own specific standard of care for ABI/TBI.		
	Created a health-cohort specific procedures flowchart.	Improved readability		
	Added exclusion of PAD cohort: – Subject may not have revascularization surgery within the last 90 day – Subject cannot lay safely in supine position	Added language to avoid ambiguity in patient symptoms and to avoid putting patient in supine position who may not be able to safely be supine for required length of time.		
	Added exclusion of Healthy cohort – Subject does not have suitable finger or toes to attach the probe – Subject is under 40 years old	Added for clarity and to ensure healthy cohort maintains an age-matched population with PAD cohort.		

	Changed FlowMet assessment procedure to note that if 5 or more repeated attempts are made with poor-quality data, then the clinician will choose the optimal record to the best of their knowledge.	Added to ensure procedure was in place for the rare occurrence where FlowMet readings cannot accurately be obtained after 5 attempts.		
	Changed date requirements of ultrasound or angiographic imaging from within 24 hours to 30 days.	Loosened this restriction to improve patient enrollment. This restriction was determined able to be reduced because very little change is expected to occur in the stenosis % in chronic PAD patients over the prior 30 days before their imaging exam. Additionally, 30 days is a commonly accepted timeframe for validity of stenosis imaging tests used in similar PAD studies.		
	MINOR CHANGES			
	Created separate event schedule C specifically for healthy cohort.	Additional language added for readability.		
	Specified patients enrolled in PAD cohort cannot be grouped into healthy cohort, even after their PAD is treated.	Always intended this way but provided additional language for clarity.		
	Request digitized copy of intraprocedural log for patient registry.	Electronic copy is required for storage in edc system.		

	Clarification that follow-up visits will be conducted as per standard of care post-procedure, and that the visits that most closely correspond to the 3- and 6- month timepoints after initial visit will be used.	Made follow up visit window less strict to better accommodate Covid situation and reduce dropout rate.		
	Inclusion Criteria: Specified that PAD cohort must meet PAD positive criteria described in protocol.	In practice this has always been the case, added explicit language for clarity		
	Added procedure if FlowMet-R system needs servicing or replacement.	Added language to improve procedure and timeline in case FlowMet system requires servicing.		
	Specified wound-specific information (wound grade, infection grade, healing status) that is required as part of medical history.	Provided additional details on medical history questions for clarity.		
	Added more specific information requests about adverse even handling (whether device related or serious).	Clarification on how to treat adverse events.		
	Added language for protocol deviation information.	Improved details for submitting protocol deviation.		