Protocol Title:

A Clinical Evaluation of the MicroSTent® PeripherAl Vascular SteNt in Subjects with Arterial Disease Below the Knee (STAND)

NCT: 03477604

A Clinical Evaluation of the MicroSTent® PeripherAl Vascular SteNt in Subjects with Arterial Disease Below the Knee (STAND)

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Sponsor:	Micro Medical Solutions, Inc. 250 Andover Street Wilmington, MA 01887

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Protocol Summary

Title	A Clinical Evaluation of the MicroStent® Peripheral Vascular Stent in Subjects with Arterial Disease Below the Knee (STAND)
Sponsor	Micro Medical Solutions, Inc. 250 Andover Street Wilmington, MA 01887
Contact Person	Amanda Panos
Study ID Number	MMS-001
Study PI	Robert E. Beasley, MD Director of Vascular/Interventional Radiology & Vein Treatment Center Director of Wound Healing Center Mount Sinai Medical Center Miami Beach, FL
Study Purpose	To evaluate the safety and effectiveness of using the MicroStent® Peripheral Vascular Stent System, hereafter referred to as the MicroStent® System, for the treatment of infrapopliteal lesions in subjects with peripheral arterial disease.
Study Design	Randomized multicenter clinical trial consisting of two arms; one arm treated with PTA plus the MicroStent® System and one arm treated with PTA alone.
Study Objectives	**Primary** Effectiveness Demonstrate treatment with the MicroStent® System is superior to PTA alone in achieving and maintaining vessel patency and improved blood flow as measured by Duplex Ultrasound (DUS). Safety Demonstrate treatment with the MicroStent® System is non-inferior to PTA alone in freedom from perioperative death and major adverse limb events (MALE) throughout the course of the study.
Study Endpoints	**Effectiveness** Primary Endpoint Primary patency defined as freedom from target lesion occlusion with no *clinically driven target lesion reintervention (TLR), or major amputation at 6 months post index procedure. * Clinically driven target lesion reintervention is defined as procedures performed to address problems that occur as a result of the index procedure and associated with complaints of continued or worsening leg pain, a progressing nonhealing ulcer, or new ulcer formation with or without the presence of an abnormal noninvasive test. (12)

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	Hypothesis Tested Secondary Endpoints 1. Freedom from major amputation (above the ankle) at 6 months post index procedure. 2. Reduction in size of ischemic leg/foot ulcers at 6 months post index intervention. Exploratory Secondary Endpoints 1. Freedom from clinically driven TLR at all timepoints. 2. Freedom from major amputation (above the ankle) at all timepoints. 3. Reduction in size of ischemic leg/foot ulcers at all timepoints. 4. Freedom from clinically driven target vessel reintervention (TVR) at all timepoints. 5. Amputation free survival at all timepoints. 6. Secondary patency defined as freedom from occlusion with or without clinically driven target lesion reintervention at all timepoints. 7. Change in lumen diameter within the lesion immediately post-treatment compared to pre-treatment as measured by angiography. 8. Peak systolic velocity ration (PSVR) patency defined as peak systolic velocity ratio ≤ 2.4 with no clinically driven target lesion reintervention at all timepoints. 9. Change in health status (measured by the EQ-5D-3L) at follow-up compared to pre-index procedure. 10. Change in daily walking ability at follow-up compared to pre-treatment as measured by the Walking Impairment Questionnaire (WIQ) 11. Change in clinical Rutherford Classification at follow-up compared to pre-treatment. 12. Change in ankle brachial index (ABI)/toe brachial index (TBI) at follow-up compared to pre-treatment. **Safety** Primary Endpoint A composite of freedom from perioperative death (POD) at 30-days and freedom from MALE at 6 months. Exploratory Secondary Endpoints 1. Freedom from MALE at all timepoints 2. Frequency and severity of serious adverse events and device and procedure-related adverse events at any time during the study.

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Study Follow-up Intervals	Follow-up at: • 30 days ±7 days • 3 months ± 2 weeks • 6 months ± 1 month • 1 year ± 2 months • 2 years ± 2 months • 3 years ± 2 months Primary endpoint data will be collected at the 6-month follow-up visit.
Follow-up Subject Activities	Physical examination, Doppler ultrasound assessment, wound assessment, amputation assessment, WIQ, and EQ-5D questionnaire.
Study Cohort	A total of 165 subjects are required for the primary analysis to achieve 80% power; 110 randomized to PTA plus MicroStent® System and 55 subjects randomized to PTA alone (2:1 randomization ratio). An additional 12 subjects will be enrolled and randomized to allow for up to 7.5% premature exit from the study. In addition, 14 subjects were treated with the MicroStent® System as part of the initial feasibility phase of the study. These are subjects who are not randomized and will not be included in the primary endpoint analysis. They will, however, undergo all follow-up visits and their data will be reported separately. Thus, a total of 192 subjects may be enrolled in the study.
Number of Investigation Sites	Up to 25 active sites in the United States
Cohort Allocation per Site	A maximum of 40 randomized subjects per site
Continuing Patient Management	Reintervention is allowed if, in the opinion of the investigator, it is in the patient's best interest. Data will be collected for all non-target lesion interventions performed post-index procedure.
Inclusion Criteria	<u>General Inclusion Criteria:</u> 1. Subject is a male or a non-pregnant female adult between the age of 21 and 90 years old. 2. Subject has documented clinical evidence of critical limb ischemia (CLI) in the target limb prior to the index procedure, with a Rutherford Classification score of 4-5. 3. The subject, or subject's designated legal representative, has been informed of the nature of the study and is willing to provide written informed consent. 4. Subject is willing to comply with all required follow-up visits. 5. Subject life expectancy is ≥1 year per the Principal Investigator. <u>Angiographic Inclusion Criteria:</u> 6. Target vessel reconstitutes at or above the ankle with inline flow to at least one patent (<50% stenosis) inframalleolar outflow vessel. 7. Subject has a lesion, with ≥ 70% stenosis and ≤ 12.0 cm in length located at or distal to the tibial-peroneal trunk and above the

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	tibiotalar joint; including the anterior tibial, posterior tibial or peroneal arteries. 8. Target lesion has a reference vessel diameter of 2.5 – 4.5 mm 9. The target lesion is able to be crossed with a guidewire to facilitate treatment with the randomized device.
Exclusion Criteria	<u>General Exclusion Criteria:</u> 1. Subject had a prior or has a planned index limb amputation above the ankle. 2. Subject has a wound/ulcer on the forefoot with a surface area >4cm² or osteomyelitis involving the calcaneus bone. 3. Subject is pregnant, plans to become pregnant, or is nursing. 4. Subject has clinical conditions that severely inhibit X-ray or duplex ultrasound visualization (e.g. body habitus). 5. Subject has a history of hypercoagulation/clotting disorders or acute thrombosis. 6. Subject has allergy to iodinated contrast media that cannot be adequately managed with medication. 7. Subject is in acute renal failure. 8. Subject has an active systemic infection. 9. Subject is participating in another research study involving an investigational device, biologic, or drug that has not completed the primary endpoint at the time of randomization/enrollment. 10. Subject has other comorbidities that - in the opinion of the investigator - preclude them from receiving study treatment and/or from completing the required study follow-up assessments. 11. Subject presents with acute limb ischemia or acute thrombosis of the target limb. 12. Subject has experienced myocardial infarction, thrombolysis, or angina less than 30 days prior to the index procedure. 13. Subject had a stroke within 3 months of index procedure. <u>Angiographic Exclusion Criteria:</u> 14. Failure to successfully treat clinically significant inflow lesions in the ipsilateral iliac, femoral, or popliteal arteries. Successful treatment is defined as obtaining ≤30% residual stenosis with no major procedural complications (e.g embolism). 15. Failure to successfully treat significant non-target infra-popliteal lesions. Successful treatment is defined as obtaining ≤30% residual stenosis with no major procedural complications (e.g. embolism). 16. Target lesion is within a previously placed stent.

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Description of Investigational Device	Self-expanding arterial stent
Data Collection & Analysis	Micro Medical Solutions, Inc.
Study Duration	16 months: primary (52 months total): 10 months for patient recruitment, 6-month primary endpoint follow-up (36 months total follow-up)
Projected Primary Study Completion Report Date	January 2021

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1.0. Introduction

1.1 Background and Rationale

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The prevalence of peripheral arterial disease (PAD) has been increasing in the developed world, with >6% of the population 65 years and older experiencing symptomatic PAD (1). Symptoms progress in severity from mild intermittent claudication to critical limb ischemia (CLI), where CLI is characterized by chronic resting leg pain, difficulty in wound healing and, eventually, amputation. It is estimated that CLI has an incidence of approximately 50 to 100 per 100,000 people per year and is associated with mortality rates as high as 20% within the first 12 months after onset (1).

Interventional cardiologists, vascular surgeons and interventional radiologists have been treating patients with severe claudication and CLI by reopening stenosed vessels with percutaneous transluminal angioplasty (PTA) balloon catheters (including drug coated balloons) as well as other devices indicated for peripheral vascular procedures. Following successful PTA, many physicians are placing metal stents to maintain luminal patency which improves blood flow.

Metallic stents used in the lower leg are either self-expanding (Nitinol) or balloon expandable systems. The safety and effectiveness of metallic stents in the vasculature is well established in both coronary and peripheral vessels above the knee (2) (3) (4) (5) (6). However, at this time there are no metallic stents approved by FDA for use in vessels below the knee (BTK). While numerous metallic stents are used every day to treat BTK vessels in CLI patients, it is not possible to accurately determine the exact number as these stents are all used off-label. The MicroStent® will be the first metallic stent clinically evaluated under an FDA approved IDE study.

More invasive procedures, such as vascular bypass surgery, may also be performed to improve blood flow to the lower extremities. However, the number of surgical bypass procedures has been on a steady decline, while the number of endovascular procedures such as PTA and stent placement has been on the rise (7).

Unlike other vascular stent procedures, patients with BTK disease may have disease in multiple vessels which require multiple procedures to improve blood flow to the lower extremities. It is not uncommon for a patient to have subsequent procedures over the course of several weeks.

From the amputee-coalition.org website, the following are some statistics regarding the CLI problem:

- There are nearly 2 million people living with limb loss in the United States
- The main causes of limb loss are vascular disease – including diabetes and PAD (54%), trauma (45%), and cancer (less than 2%).
- Approximately 185,000 amputations occur in the United States each year.
- Hospital costs associated with having a limb amputated totaled more than $8.3 billion in 2009
- Survival rates after an amputation vary based on a variety of factors. Those who have amputations due to vascular disease (including PAD and diabetes) face a 30-day mortality rate reported to be between 9 -15% and a long-term survival rate of 60% at 1 year, 42% at 3 years, and 35-45% at 5 years.

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- Nearly half of the people who lose a limb to vascular disease will die within 5 years. This is higher than the 5-year mortality rate experienced by people with colorectal, breast, and prostate cancer.
- Of people with diabetes who have a lower-limb amputation, up to 55% will require amputation of the second leg within 2 to 3 years.

1.2 Summary of Prior Investigations

1.2.1 Animal Studies

Micro Medical Solutions (MMS) conducted animal studies during the development of the MicroStent® System including a chronic GLP study at CBSET Inc. (Lexington MA). The objective of the GLP study was to evaluate the tissue response to implantation with the MicroStent® System. Angiography and histologic evaluation of the implants were used to assess healing response at the implant site at time points up to 90 days. Acute performance characteristics of the stent and delivery system were also assessed at the time of implantation.

Thirty MicroStents® were successfully implanted into the superficial femoral artery (SFA) of 15 Swine. There were no dissections caused by the stent or delivery system and no thrombus was observed on the catheter when removed from the guiding sheath. Acute handling in the non-tortuous iliofemoral arteries was favorable as graded by the interventionalist. Trackability and radiopacity of the MicroStent® System was graded average or above average. The stent deployment characteristics, stent conformity to the vessel, and ability to post dilate also scored average or above average. Visualization of the stent under fluoroscopy was average, and typical for peripheral artery stents. Mild to severe vasospasm was observed post implant in most of the Yucatan mini swine but was not flow limiting. Vasospasm was rarely observed in the Yorkshire swine. There were no adverse health effects and all animals survived to their scheduled endpoint.

Total occlusion was observed at the endpoint in 7 of 30 implanted stents (2 stents at Day 3 and 5 stents at Day 30). These occlusions were only observed in the Yucatans, all stents in the Yorkshire swine were patent. Angiography showed irregular expansion of the stents likely in conformation of the vessel wall. These stents were removed from group summary data and reported separately.

After 3, 30, and 90 days neointimal responses were <50% by angiography at all time points. Histologic assessment of non-occluded vessels indicated injury was absent at Day 3, and nearly absent and overall minimal at Day 30 and Day 90. Inflammation was minimal at all time points, with scores nearly always Grade 1. Inflammatory infiltrates were predominantly neointimal, with neutrophils most common at Day 3 and histiocytes and giant cells at Day 90. Neointimal fibrin was minimal or absent at Day 30 and nearly absent at Day 90. Neointima was mature at Day 30 and Day 90, at which time adventitial fibrosis-fibroplasia was minimal or absent, and endothelialization complete. There was negligible narrowing of implanted arteries at Day 3 (12% stenosis), mild increase from Day 3 to Day 30 (~30% stenosis) and were nearly unchanged from Day 30 to Day 90. There was no necrosis or embolism in downstream muscle sections.

Standard histomorphologic parameters associated with occluded vessels were comparable to those seen in non-occluded vessels, and there was no evidence that occlusion was caused by vascular injury or inflammation. Malapposition of the proximal stent edge was identified in 1 of 2 of these Day 3 animals and 5/5 of the Day 30 vessels which likely resulted in thrombus formation.

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There were consistent and macroscopically evident occlusive and/or neointimal responses in all four animals of the Day 30 Yucatan group (G2), considered mostly likely to represent mechanical variables (e.g., incomplete deployment or subsequent constriction of stent struts). Occlusion did not occur in the Yorkshire swine so a relation to the Yucatan mini swine model cannot be ruled out.

1.2.2 Feasibility Study

Micro Medical Solutions (MMS) conducted a non-randomized multicenter clinical feasibility trial consisting of one arm treated with PTA plus the MicroStent® Peripheral Stent System. 15 subjects were enrolled at 3 centers in the United States. The primary objectives of the MicroStent® Peripheral Vascular Stent in Subjects with Artery Lesions below the Knee Feasibility Study are to evaluate the safety and technical feasibility of the MMS MicroStent® Peripheral Stent System with PTA in the treatment of lower limb arterial lesions. Short-term device efficacy is assessed by achievement and maintenance of vessel patency and improved blood flow as measured by Duplex Ultrasound (DUS) at 30 days post-index procedure and clinical safety is measured by the incidence of Major Adverse Limb Events and Perioperative death through 30 days post-index procedure. Subject follow-up was immediately post-treatment, 14 ± 2 days, 30 ± 5 days, 3 months ± 2 weeks, 6 months ± 1 month, and 1 year ± 2 months. Annual follow up for the next 2 years.

Prior to initiation of the index procedure, the investigator or a designated member of his/her staff performed a review of the subject's medical history and/or performed a physical exam or other evaluation to determine the subject's eligibility for the study. Eligible subjects were approached by the investigator or a designated member of his/her staff to discuss, review and sign the Informed Consent. Final subject eligibility was determined during the endovascular procedure on consented subjects.

Prior to gaining access, two radiopaque rulers were affixed to the index limb to allow for adequate calibration and documentation of angiographic measurements by the core lab. Vascular access was gained via institutional standard and/or investigator preference. Upon successful access, an angiogram was completed to assess the eligibility of the subject with regards to infra-popliteal lesion characteristics and the presence of concomitant inflow disease requiring treatment.

Successful treatment of inflow lesions and / or infra-popliteal lesions not meeting study criteria were required prior to enrollment into the feasibility study, defined as attainment of ≤30% residual stenosis by visual estimate. If the subject was confirmed to meet all prior eligibility requirements, final subject eligibility is confirmed when the target lesion is crossed with a guidewire, after which the subject was treated with the MMS System and will be considered enrolled in the feasibility study.

Primary Safety and Efficacy Endpoints from the MicroStent® Feasibility Study demonstrates good initial safety and efficacy of the MMS MicroStent® Peripheral Stent System with promising results in the primary treatment of lower limb arterial lesions. The primary efficacy and safety endpoints were evaluated using the intent-to-treat (ITT) population of study subjects. The robustness of study results was evaluated using the per protocol (PP) population of all subjects who complete the study without major protocol violations. At the 30-day timepoint, 100% of subjects satisfied the primary safety endpoint in both the ITT and

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PP populations for all cause and device-related events. At the 30-day timepoint, the PP population satisfied 91.7% device-related and 83.3% all cause primary efficacy endpoint. At the 30-day timepoint, the ITT population satisfied 78.6% device-related and 71.4% all cause primary efficacy endpoint.

1.3 Risks and Benefits

1.3.1 Risks

The associated risks proposed in this study are similar to risks posed by other interventional and vascular surgery procedures.

Adverse events that may possibly be caused by or associated with the use of the investigational device or the related procedures, and which may or may not require endovascular or surgical treatment in this clinical trial include:

- Allergic response
- Arterial occlusion
- Arterial thrombus
- Arterio-venous fistula (unplanned)
- Bleeding/oozing from the puncture site
- Bruising at wound site
- Contrast-induced nephropathy and renal failure
- Compartment syndrome
- Congestive cardiac failure
- Death
- Device failure / malfunction
- Edema
- Embolization (air, tissue, device)
- Hematoma
- Infection
- Inflammatory response
- Intimal tear / dissection
- Lower extremity ischemia
- Occlusion of the Stent
- Peripheral nerve injury
- Perforation of the vessel wall
- Pseudoaneurysm
- Retroperitoneal bleeding
- Venous thrombus formation
- Vasovagal response
- Vasospasm
- Vascular injury
- Wound dehiscence
- Wound site pain
- Systemic infection, sepsis
- Requirement for major amputation of index limb

Risks to the patient are minimized due to:

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- The devices use well known medical grade materials that have been thoroughly tested to assure biocompatibility.
- The products are packaged in medical grade packaging and sterilized in a validated sterilization cycle. The products are supplied sterile.
- Extensive pre-clinical evaluation including in vitro bench testing, animal and cadaver study to evaluate the safety of the device.
- The well-established, standard nature of the endovascular procedures and techniques to be used.
- Frequent follow-up visits are conducted in the first year post-operatively to allow for systematic monitoring and surveillance of the index limb, allowing for early detection of hemodynamically significant stenoses that may occur in the absence of obvious symptoms.

1.3.2 Benefits

The benefit to the subjects enrolled in this study is the potential for improved blood flow to the lower limb and foot. Improved blood flow helps reduce limb ischemia, improves wound healing and reduces the chance for amputation.

In addition, the physician has the ability to, prior to stent delivery, quickly and safely remove the MicroStent® System from the procedure; the physician may elect to discontinue the use of the device at any time in favor of alternate devices.

2.0. Device Description and Labeling

2.1 Device Description

The MicroStent® System is comprised of a self-expanding, woven nitinol stent (the MicroStent®) pre-loaded into a delivery system. The delivery system is comprised of the MicroGuide® catheter (cleared under K152625). with the addition of a stabilizer assembly to allow for deployment of the MicroStent® via a 'pin-and-pull' technique.

The MicroStent® System is intended to improve luminal diameter in the treatment of ischemia in the lower leg with reference vessel diameters ranging from 2.5 mm - 4.5 mm. See Table 1 for stent sizing recommendations.

Table 1. Stent diameter sizing recommendations.

Stent Diameter Selection Table	
Reference Vessel Diameter	Stent Size
2.5-3.0mm	3.0mm
3.0-3.5mm	3.5mm
3.5-4.0mm	4.0mm
4.0-4.5mm	4.5mm

Table 2. Delivery System

Delivery System Lengths
40 cm
120 cm

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Table 3. Stent foreshortening lengths by diameter.

Foreshortening Table		
Stent Size	Vessel Diameter	Stent Length
3.0x15mm	2.5mm	23mm
	3.0mm	19mm
3.0x25mm	2.5mm	39mm
	3.0mm	33mm
3.0x40mm	2.5mm	62mm
	3.0mm	51mm
3.0x60mm	2.5mm	93mm
	3.0mm	77mm
3.5x15mm	3.0mm	25mm
	3.5mm	21mm
3.5x25mm	3.0mm	42mm
	3.5mm	35mm
3.5x40mm	3.0mm	67mm
	3.5mm	56mm
3.5x60mm	3.0mm	101mm
	3.5mm	84mm

Foreshortening Table		
Stent Size	Vessel Diameter	Stent Length
4.0x15mm	3.5mm	27mm
	4.0mm	23mm
4.0x25mm	3.5mm	45mm
	4.0mm	37mm
4.0x40mm	3.5mm	73mm
	4.0mm	61mm
4.0x60mm	3.5mm	110mm
	4.0mm	92mm
4.5x15mm	4.0mm	30mm
	4.5mm	25mm
4.5x25mm	4.0mm	48mm
	4.5mm	39mm
4.5x40mm	4.0mm	79mm
	4.5mm	67mm
4.5x60mm	4.0mm	119mm
	4.5mm	100mm

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The MicroStent®

The stent (Figure 1) is formed from nitinol wires in a braided design. Upon deployment, the stent achieves its predetermined diameter and exerts a constant, gentle outward force to establish and maintain patency. The stent wires have a radiopaque platinum core that provides improved visibility of the braided stent during deployment and subsequent follow-up.

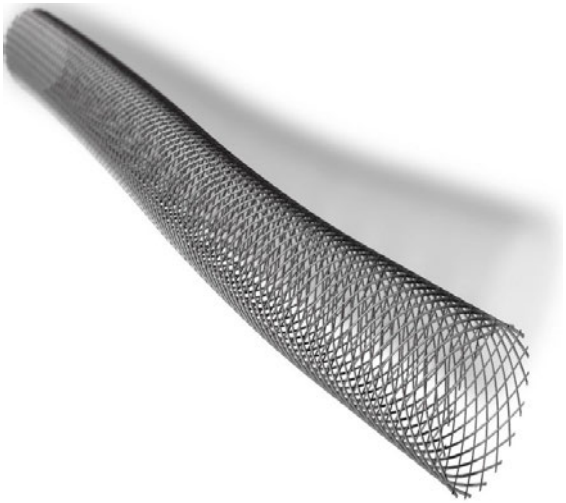


Figure 1*. MicroStent® Component of the MicroStent® System*

The Delivery System

The delivery system (Figure 2) includes a 3.2F catheter with a coaxial inner assembly (stent stabilizer). A proximal Tuohy-Borst valve on the catheter provides hemostasis as well as a safety lock to prevent premature deployment of the stent. The stent stabilizer terminates distally through the pre-loaded stent and out the distal end of the catheter. The distal portion of the catheter contains a radiopaque marker to demarcate the distal placement of the stent, while the stent stabilizer also has a radiopaque maker to demarcate the proximal placement of the stent. The MicroStent® is constrained within the space between the stent stabilizer and the catheter. This space is flushed prior to the procedure through the side port in the Tuohy-Borst valve.



Figure 2*. Delivery System Component of the Peripheral Stent System*

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The 3.2 F MicroGuide® catheter is the main component of the delivery system. The stent stabilizer is loaded into the MicroGuide®, with the MicroStent®, to make up the MicroStent® System. The MicroGuide® (40 cm) is a 510(k) cleared (K152625) medical device in the United States and the MicroStent® System was CE Marked (Certificate No. 31132) in the European Union on 08April2016. The MicroGuide® (120 cm) and MicroStent® System was added to CE Mark (Certificate No. 31132) in the European Union on 11October2018.

Stent Deployment

The stent is positioned at the target lesion using the radiopaque markers on the distal end of the catheter and the stent stabilizer. For stent deployment, the proximal valve is loosened to unlock the stent stabilizer. The catheter is retracted by pinning the proximal stent stabilizer and pulling the Tuohy-Borst valve on the catheter toward it. Stent deployment is complete when the distal radiopaque marker on the catheter passes the proximal end of the stent and reaches the radiopaque marker on the stent stabilizer.

2.2. Intended Use

The MicroStent® System is intended to improve luminal diameter in the treatment of ischemia in the lower leg with reference vessel diameters ranging from 2.5 mm - 4.5 mm.

2.3. Device Labeling

A copy of the Instructions for Use (IFU) will be included with the devices. The MicroStent® System labeling will include the following information relative to the MicroStent® device.

- Lot or Serial number
- Expiration (use before) date
- For Investigational Use Only

3.0. Study Objectives

3.1. Primary

<u>Effectiveness</u>

Demonstrate treatment with the MicroStent® System is superior to PTA alone in achieving and maintaining vessel patency and improved blood flow as measured by Duplex Ultrasound (DUS).

<u>Safety</u>

Demonstrate treatment with the MicroStent® System is non-inferior to PTA alone in freedom from perioperative death and MALE throughout the course of the study.

4.0. Study Design

The study is a randomized multicenter clinical trial consisting of two arms; one arm treated with PTA plus the MicroStent® System and one arm treated with PTA alone.

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All target lesions will be numbered with a unique number including the subject number to allow accurate data collection. Data analysis will be for subject as well as individual lesion. Follow-up intervals will be based on the index procedure with observations for any additional interventions recorded.

A core lab will be used for the angiography and ultrasound images. Wound healing will be assessed by use of wound camera that calculates data supporting wound improvment or deterioration. .

4.1. Overview

The study is a randomized controlled multicenter clinical trial consisting of two arms; one arm treated with PTA plus the MicroStent® System and one arm treated with PTA alone. The MicroStent® System (investigational device) results will be compared to the control arm (standard PTA) to assess the safety and effectiveness of using a self-expanding stent for the treatment of infrapopliteal lesions in subjects with peripheral arterial disease.

4.2. Number of Subjects and Investigational Sites

A total of 165 subjects are required for the primary analysis to achieve 80% power; 110 randomized to PTA plus MicroStent® System and 55 subjects randomized to PTA alone (2:1 randomization ratio). An additional 12 subjects will be enrolled and randomized to allow for up to 7.5% premature exit from the study. In addition, 15 subjects were treated with the MicroStent® System as part of the initial phase of the study. These are subjects who are not randomized and will not be included in the primary endpoint analysis. They will, however, undergo all follow-up visits and their data will be reported separately. Thus, a total of 192 subjects may be enrolled in the study. Subject recruitment will take place at up to 25 active investigational sites in the United States. Investigational sites may enroll up to 40 subjects each.

5.0. Study Population

5.1. Selection Criteria

The following section outlines the specific inclusion and exclusion criteria for the study. Before enrollment, a patient must meet all the inclusion and none of the exclusion criteria.

5.1.1. Inclusion Criteria

<u>General Inclusion Criteria:</u>

1. Subject is a male or a non-pregnant female adult between the age of 21 and 90 years old.
2. Subject has documented clinical evidence of critical limb ischemia (CLI) in the target limb prior to the index procedure, with a Rutherford Classification score of 4-5.
3. The subject, or subject's designated legal representative, has been informed of the nature of the study and is willing to provide written informed consent.
4. Subject is willing to comply with all required follow-up visits.
5. Subject life expectancy is ≥1 year per the Principal Investigator.

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Angiographic Inclusion Criteria:

6. Target vessel reconstitutes at or above the ankle with inline flow to at least one patent (<50% stenosis) inframalleolar outflow vessel.
7. Subject has a lesion, with ≥ 70% stenosis and ≤ 12.0 cm in length located at or distal to the tibial-peroneal trunk and above the tibiotalar joint; including the anterior tibial, posterior tibial or peroneal arteries.
8. Target lesion has a reference vessel diameter of 2.5 – 4.5 mm
9. The target lesion is able to be crossed with a guidewire to facilitate treatment with the randomized device.

5.1.2. Exclusion Criteria

General Exclusion Criteria:

1. Subject had a prior or has a planned index limb amputation above the ankle.
2. Subject has a wound/ulcer on the forefoot with a surface area >4cm² or osteomyelitis involving the calcaneus bone.
3. Subject is pregnant, plans to become pregnant, or is nursing.
4. Subject has clinical conditions that severely inhibit X-ray or duplex ultrasound visualization (e.g. body habitus).
5. Subject has a history of hypercoagulation/clotting disorders or acute thrombosis.
6. Subject has allergy to iodinated contrast media that cannot be adequately managed with medication.
7. Subject is in acute renal failure.
8. Subject has an active systemic infection.
9. Subject is participating in another research study involving an investigational device, biologic, or drug that has not completed the primary endpoint at the time of randomization/enrollment.
10. Subject has other comorbidities that - in the opinion of the investigator - preclude them from receiving study treatment and/or from completing the required study follow-up assessments.
11. Subject presents with acute limb ischemia or acute thrombosis of the target limb.
12. Subject has experienced myocardial infarction, thrombolysis, or angina less than 30 days prior to the index procedure.
13. Subject had a stroke within 3 months of index procedure.

Angiographic Exclusion Criteria:

14. Failure to successfully treat clinically significant inflow lesions in the ipsilateral iliac, femoral, or popliteal arteries. Successful treatment is defined as obtaining ≤30% residual stenosis with no major procedural complications (e.g embolism).
15. Failure to successfully treat significant non-target infra-popliteal lesions. Successful treatment is defined as obtaining ≤30% residual stenosis with no major procedural complications (e.g. embolism).
16. Target lesion is within a previously placed stent.

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6.0. Study Procedures and Enrollment

6.1. Duration of Subject Participation and Visit Overview

Subjects enrolled in the study will participate for approximately 3 years (± 2 months).

Study assessments to be performed at each visit are summarized in Table 4.

Table 4. Assessments performed at each study visit.

Assessments	Screening/ Baseline	Procedure	30 days (± 7 days)	3 months (± 2 wks)	6 months (± 1 mo)	1 year (± 2 mo)	2 year (± 2 mo)	3 year (± 2 mo)
Subject Eligibility	X							
Subject Demographics	X							
Medical History	X							
Surgical Interventional History	X							
Adverse Event Assessment		X	X	X	X	X	X	X
Amputation Assessment			X	X	X	X	X	X
Procedure Imaging Worksheet (e.g. Angiography, DUS, IVUS, etc)		X						
Concomitant Meds Assessment	X	X	X	X	X	X	X	X
Ultrasound Assessment			X	X	X	X	X	X
End of Study/Withdrawal								X
EQ-5D	X		X	X	X	X	X	X
Physical Exam (Incl. ABI/TBI and Rutherford Assessment)	X		X	X	X	X	X	X
Procedure and Device Details		X						
Reintervention Assessment			X	X	X	X	X	X
Walking Impairment Questionnaire	X		X	X	X	X	X	X
Wound Assessment	X		X	X	X	X	X	X

6.2. Study Procedures

6.2.1. Screening Evaluations

Informed Consent

All subjects considered for inclusion in this study should have the study explained to them, be given the IRB-approved informed consent form, and allowed adequate time to consider whether or not they wish to take part in the study. The investigator or delegated member of his/her staff should inform the patient about the study's purpose, the risks and benefits of participation, and availability of alternative treatments. The patient must be able to ask questions regarding the study and have their questions addressed during this process. Written informed consent must be obtained for all patients who are potential study candidates before any study-specific tests or procedures are performed.

If the subject is willing to participate in the clinical investigation, he/she or an authorized legal representative with Power-of-Attorney (POA) must sign and date the informed consent form indicating that they have read and understood the information provided. Documentation of this relationship must be provided. Each site will follow their local IRB and applicable regulatory guidelines for obtaining informed consent. Documentation of the informed consent

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process for each subject and the original signed informed consent will be retained at the site and as required by applicable regulations.

Pre-procedural Subject Eligibility

Prior to initiation of the index procedure, the investigator or a designated member of his/her staff will perform a review of the subject's medical history and/or perform a physical exam or other evaluation to determine the subject's general eligibility for the study.

Baseline Data Collection

If the subject is deemed to be a good candidate and has given informed consent, baseline characteristics including subject demographics, medical history, surgical and endovascular intervention history, and concomitant medications will be collected. The baseline examination will include a physical exam, collection of ABI/TBI measurements, and completion of the EQ-5D and WIQ questionnaires.

Baseline Wound Assessment

Any wounds present on the target limb will be photographed using a commercially available, FDA registered Wound Camera which captures an image and calculates the area of the wound. Wounds will be assigned a number at the baseline visit to facilitate follow-up assessments. Photographs are to include medial and lateral projections of the dorsum of the foot, including the toes, as well as medial and lateral projections of the plantar aspect of the foot if applicable. The artery(ies) perfusing the angiosome where the wound is located should be documented.

6.2.2. Study Procedure

Subject Eligibility and Randomization

Final subject eligibility will be determined during the endovascular index procedure. A radiopaque ruler will be affixed to the index limb to allow for adequate calibration and documentation of angiographic measurements by the core lab. Vascular access will be gained via institutional standard and/or investigator preference. Upon successful access, an angiogram will be completed to assess the angiographic eligibility of the subject with regards to infrapopliteal lesion characteristics and the presence of concomitant inflow disease requiring treatment.

Successful treatment of clinically significant inflow lesions and/or clinically significant infrapopliteal lesions not meeting study criteria are required *prior* to randomization/enrollment into the investigational study, defined as attainment of ≤30% residual stenosis by visual estimate without major complications. Treatment of clinically significant in-line outflow lesions should be performed at the time of index procedure. Treatment of inflow, outflow, and non-target lesions, in non-target vessels is allowed with the use of on-label devices only; however, the use of alternative therapies such as atherectomy, cryoplasty, cutting/scoring/plaque modifying balloons, or drug coated balloons is not allowed within the target lesion unless required for bailout purposes. Angiographic images of inflow and outflow arteries must be captured to confirm eligibility, and the presence or absence of an intact pedal arch should be documented.

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If the subject has been confirmed to meet all prior general eligibility requirements, final subject angiographic eligibility is confirmed when the target lesion is crossed with a guidewire, after which the subject will be randomized to treatment with the MicroStent® System or PTA alone. The subject will be considered enrolled in the study upon randomization. Adverse Event collection will begin at time of enrollment.

A 2:1 randomization ratio will be utilized to randomize 2 subjects to the MicroStent® System arm for every 1 subject randomized to the PTA only arm. Permuted blocks will be used to maintain a 2:1 ratio across all study sites. Randomization will be completed within the study electronic data capture (EDC) system.

Index Study Treatment

After randomization, the target lesion will be treated in accordance with the IFU for the randomized device.

For the PTA arm, primary treatment with a standard balloon catheter will be completed per balloon IFU. Balloon nominal diameter, length, maximum inflation pressure, total inflation time, and the total number of inflations will be recorded for the lesion treated. In the case of sub-optimal outcomes after treatment with standard PTA, bailout procedures are allowed at the discretion of the investigator, however the use of the MicroStent is not allowed in a bailout procedure. Sub-optimal PTA outcomes are confined to the following criteria:

- Flow limiting dissection (e.g. ≥ Grade C) or vessel perforation that is not amenable or responsive to two prolonged balloon inflation (≥2 min each).
- Acute vessel recoil or other negative occlusive complication that results in severely decreased vessel blood flow
- Persistent residual stenosis ≥30% by visual estimate after two prolonged balloon inflations

Subjects requiring bailout procedures to obtain clinically acceptable outcomes will be considered a primary patency failure for the purposes of this study. The Clinical Events Committee (CEC) will review procedural angiograms to verify the use of a bailout procedure was appropriate.

The MicroStent® System, should be placed per the IFU. If performed, post stent dilation should be performed utilizing a balloon catheter that matches the size of the reference vessel, but that is not larger than the stent diameter itself.

If the subject has a wound on the target limb, the artery(ies) perfusing the angiosome where the wound is located should be documented. For each arm, angiographic images of the target lesion in two orthogonal views will be collected for each of the following: prior to randomization/enrollment to establish eligibility, after PTA treatment (primary treatment for PTA arm, pre-dilatation for MicroStent® Stent arm), after stent placement to verify successful deployment, and at the close of the procedure (final). Angiographic images should also be captured during inflation of the PTA balloon (pre and post-dilation as applicable) as well as during stent deployment to aid the core lab in defining the target lesion and treated regions.

Operator Assessment of Successful Stent Deployment, i.e., implanted stent provides coverage of the lesion as intended. The operator will also angiographically document

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those criteria required by the angiographic core lab to assess accuracy (e.g., lesion endpoints, desired stent landing points).

Core Lab Assessment of Successful Stent Expansion, Deployment Accuracy, and Stent Foreshortening, which will include review of angiographic films by the Angiographic Core Lab.

6.2.3. Follow-up

Subjects should return to the clinic at 30 days (± 7 days), 3 months (± 2 weeks), 6 months (± 1 month), 1 year (± 2 months), 2 years (± 2 months), and 3 years (± 2 months) post index procedure.

Physical Examination and Quality of Life

Routine surveillance of the subject will be performed during each follow-up visit consistent with ACC/AHA 2016 Peripheral Disease Guidelines (13). Examinations will include assessments of quality of life metrics (e.g. EQ-5D and WIQ questionnaires), blood pressure, heart rate, height/weight/body mass index (BMI), Rutherford Classification, ABI, TBI, wound size/healing status, medication regimen and any procedures, serious adverse events, or adverse events related to the device and procedure occurring since the last visit.

Wound Assessment

At each follow-up visit, any wounds will be photographed using a commercially available, FDA registered Wound Camera which captures an image and calculates the area of the wound. Photographs are to include medial and lateral projections of the dorsum of the foot, including the toes, as well as medial and lateral projections of the plantar aspect of the foot if applicable.

Duplex Ultrasound Examination

A DUS exam will be performed at the 30-day, 3-month, 6-month, 1-year, 2-year, and 3-year visits, including all reinterventions and unscheduled visits to assess the following:

1. Target lesion patency as determined by the presence or absence of flow
2. Blood flow velocity proximal to, within, and distal to the target lesion for the purposes of determining the PSVR
3. Patency throughout the target limb (inflow and outflow of the target lesion) as determined by the presence or absence of flow.

A DUS core lab will evaluate results from all DUS examinations and determine target lesion patency, blood flow velocity and PSVR. Target lesion patency and blood flow/PSVR will be determined for the target lesion at each timepoint requiring DUS.

6.2.4. Study Exit

During the course of the clinical investigation, subjects will be or may elect to be withdrawn from study participation for including but not limited to the following reasons:

a. Subject has completed all required follow-up visits;
b. Subject has withdrawn consent to participate in the study;
c. Subject is lost to follow-up;
d. Subject is deceased;
e. Any problem deemed by the Principal investigator and/ Sponsor name to be sufficient to cause discontinuation.

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All subjects discontinued from the clinical investigation due to an unexpected adverse device effect (UADE) directly related to the investigational device will be treated until the effect resolves.

Subjects who are withdrawn or lost to follow-up after randomization will not be replaced. If possible, any procedures or assessments planned for the subject on withdrawal from the clinical investigation should be performed when intention to withdraw the subject is announced. For subjects lost to follow-up, a minimum of 3 attempts must be made (and documented appropriately in source) to contact the subject prior to withdrawal from the study.
Subjects who are withdrawn prior to randomization will be replaced.

7.0. Assessment of Safety and Effectiveness

7.1. Primary Safety Endpoint

A composite of freedom from POD at 30-days and freedom from MALE at 6-months post index procedure.

7.2. Secondary Safety Endpoints

1. Freedom from MALE at all timepoints
2. Frequency and severity of serious adverse events and device and procedure-related adverse events at any time during the study.

7.3. Primary Effectiveness Endpoint

Primary patency defined as freedom from target lesion occlusion with no *clinically driven TLR, or major amputation at 6-months post index procedure.

* clinically driven target lesion reintervention is defined as procedures performed to address problems that occur as a result of the index procedure and associated with complaints of continued or worsening leg pain, a progressing nonhealing ulcer, or new ulcer formation with or without the presence of an abnormal noninvasive test. (12)

7.4. Secondary Effectiveness Endpoints

Hypothesis Tested Secondary Endpoints:

1. Freedom from major amputation (above the ankle) at 6-months post index procedure.
2. Reduction in size of ischemic leg/foot ulcers at 6-months post index procedure.

Exploratory Secondary Endpoints:

1. Freedom from clinically driven TLR at all timepoints.
2. Freedom from major amputation (above the ankle) at all timepoints.
3. Reduction in size of ischemic leg/foot ulcers at all timepoints.
4. Freedom from clinically driven TVR at all timepoints.
5. Amputation free survival at all timepoints.

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6. Secondary patency defined as freedom from occlusion with or without clinically driven target lesion reintervention at all timepoints.
7. Change in lumen diameter within the lesion immediately post-treatment compared to pre-treatment as measured by angiography.
8. PSVR patency defined as peak systolic velocity ratio ≤ 2.4 with no clinically driven device-related target lesion reintervention at all timepoints.
9. Change in health status (measured by the EQ-5D-3L) at follow-up compared to pre-treatment.
10. Change in daily walking ability at follow-up compared to pre-treatment as measured by the WIQ
11. Change in clinical Rutherford category at follow-up compared to pre-treatment.
12. Change in ABI/TBI at follow-up compared to pre-treatment.

8.0. Adverse Event Reporting

8.1. General Definitions

Adverse Event (AE) - An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject whether or not it is considered to be device or procedure-related. In addition, the definition of AE applies to any untoward medical event with an onset post study procedure or to any underlying diseases, present at baseline that exacerbate in severity post study procedure. Therefore, an underlying disease that was present at the time of enrollment is not reported as an AE, but any increase in the severity of the underlying disease is to be reported as an AE.

Serious Adverse Event (SAE) – A serious adverse event is any adverse event that:

- led to a death;
- led to a serious deterioration in the health of the subject that
    - results in a life-threatening illness or injury;
    - results in a permanent impairment of a body structure or a body function;
    - requires inpatient hospitalization (>24hrs) or prolongation of existing hospitalization;
    - results in medical or surgical intervention to prevent permanent impairment to body structure or a body function; or
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

Procedure-Related Adverse Event: Events that occur from the procedure, irrespective of the device, as determined by the Principal Investigator. (12)

Device-Related Adverse Event: Events directly attributable to the device itself, as determined by the Principal Investigator. (12)

Serious Adverse Device Effect (SADE) – an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event is considered a serious adverse device effect.

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Unanticipated Adverse Device Effect (UADE): Any serious adverse device effect which was not previously identified in nature, severity, or degree of incidence in the applicable product information (Clinical Investigational Plan, IFU, etc.).

The severity of adverse events will be determined by the Principal Investigator using the following definitions:

Mild:	Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs or symptoms are transient.
Moderate:	Interferes with the subject's usual activity and/or requires symptomatic treatment.
Severe:	Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and/or are disabling or life threatening; requires treatment.

The relationship to the study device and study procedure will be determined by the Principal Investigator using the following definitions (12):

Device-Related:	The event is device-related if it could not be expected to occur even when the device performs at 100% of expectations.
Procedure-Related:	Any non device-related adverse events that occur ≤30 days of device implantation are procedure-related.
Non-device and non-procedure-related:	All other events which are neither device-related nor procedure-related based upon the above definitions.

Table 4: Basic Principles for Reporting Adverse Events (12)

Basic Principles for Reporting Adverse Events	
Scenario	**Reporting standards**
Types of adverse events to report	Report only those events that occur after the use of a medical device or after interventions performed in preparation for the use of the device.
Reporting of pre-existing diseases	Pre-existing disease states should not be reported as adverse events unless they worsen after implantation of a device.
How does one draw the distinction between device-relatedness vs procedure-relatedness?	The event is not device-related if it could be expected to occur even when the device performs at 100% of expectations. If such events occur ≤30 days of device implantation, they are considered to be procedure-related; all others are neither device-related nor procedure-related.

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What about unrelated interventions performed after implantation of a device?	Interventions performed for stable disease states do not constitute adverse events with respect to an unrelated medical device under study.
	Interventions for worsening of a pre-existing disease state, although not adverse events themselves, should trigger reporting of the adverse event that prompted the intervention.
Reporting of events occurring ≤30 days of device implantation?	Any non device-related adverse events that occur ≤30 days of device implantation are, by convention, procedure-related.
Reporting of additional procedures occurring after medical device implantation?	When an additional procedure is performed after implantation of a device, a new or worsened disease state that prompted the additional procedure is coded as the adverse event, not the procedure itself.
Which procedures could be considered reinterventions?	Procedures performed to address problems that occur as a result of the index procedure are considered reinterventions. Purely diagnostic procedures are not included in this definition.
Is a reintervention considered an adverse event?	Reinterventions themselves are not adverse events. The complication underlying the reintervention is the adverse event.
Is an unplanned procedure at the time of the index procedure an adverse event? Is it a reintervention?	The procedure itself is not an adverse event, but the untoward occurrence that prompted the event is tabulated. If a procedure is performed in the same sitting as the index procedure, it is considered a reintervention if undertaken to address the primary indication for the index procedure.

8.2. Documentation of Adverse Events

All events will be documented by the Principal Investigator on the appropriate source document(s) at the investigational site and also on the Adverse Event CRF. Adverse events are to be recorded and dated according to when they are first observed, and all subsequent treatment(s) should also be documented. The following will be recorded on the Adverse Event CRF:

- The accepted medical term for the event;
- Description of the event;
- Date of onset;
- Date of resolution if applicable;
- Outcome;
- Treatment(s)/action(s) taken;
- Severity
- Relationship to the study device or procedure

In addition, it is the investigator's responsibility to determine whether the adverse event is reportable to the sponsor or local IRB per Section 8.3 of this protocol or local IRB policy. MMS, in cooperation with the investigator, will assess all adverse events considered to be adverse

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device effects for potential reportability to the FDA and other regulatory authorities as an Unanticipated Adverse Device Effect (UADE).

The investigator should follow all unresolved serious adverse events until the events are resolved, the subject is lost to follow-up, the subject has withdrawn consent, or the adverse event is otherwise explained.

For purposes of this study, the following events are not considered adverse events, because they are normally expected to occur in conjunction with endovascular procedures/post-procedure, or are associated with customary, standard care of subjects undergoing these procedures:

- Early post-operative pain (within 48 hours post-index procedure) at the access site and/or related to position on procedure table
- Post-anesthesia/conscious sedation emesis, nausea, or headache (within 48 hours post-index procedure)
- Chest pain without associated ECG changes
- Hematocrit decrease from baseline not associated with hemodynamic changes, remaining above 30% and not requiring transfusion
- Electrolyte imbalance without clinical sequelae following endovascular procedure, even if requiring correction
- Low grade temperature increase (≤38.3°C/≤101°F)
- Sinus bradycardia/tachycardia that does not require treatment or intervention
- Systolic or diastolic blood pressure changes that do not require treatment or intervention

This listing of events is intended to provide guidance to the investigational sites for purposes of adverse event reporting. The investigator at the investigational site should utilize his/her own clinical judgment in evaluating adverse experiences and may decide that the above events should be reported as adverse events.

8.3. Reporting of Serious and Non-Serious Adverse Events

8.3.1. General Reporting Requirements

All applicable adverse events (see Section 8.2) will be reported and monitored from the time of treatment through the 3-year follow-up visit.

In the case of SAEs and/or device failures or malfunctions, and device-related events, redacted medical record documentation (e.g. procedure notes, operative notes, discharge summary, relevant progress notes, imaging or lab studies) must be provided to sponsor or its designee upon request.

8.3.2. Reporting to Sponsor

All SAEs, SADEs, and UADEs and any device malfunctions or failures should be reported by the investigator (or designee) to the sponsor within 24 hours of awareness by completion of the Adverse Event CRF. Alternatively, the investigator may contact the sponsor directly within 24 hours of awareness:

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Sponsor Contact:

STANDtrial@micromedicalsolutions.net

The Sponsor shall report results of their evaluations of UADEs to the FDA, all reviewing IRBs, and all participating Investigators within 10 business days after the Sponsor/Sponsor representative is first made aware of the event.

8.4. Device Failures and Malfunctions

Device performance will be evaluated by the treating physician. All performance data will be captured on the case report forms.

Device Failure: A device has failed if it does not perform according to labeling and negatively impacts the treatment while used according to the labeling.

Device Malfunction: A device malfunction is an unexpected change to the device that is contradictory to the labeling and may or may not affect device performance.

All reported device malfunctions or failures are required to be documented in the CRF. In the event of a device failure or malfunction, the investigational device shall be returned to the Sponsor for examination. Device failures and malfunctions should also be documented in the subject's medical record. Instructions for returning the investigational device are included in the Manual of Operations.

NOTE: Device failures or malfunctions are NOT to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded in the CRF.

9.0. Statistical Considerations

9.1. Considerations for the Control of Bias

Blinding: Blinding of subjects, investigators, ultrasound technicians and core lab personnel evaluating ultrasound images is impossible and will not be a feature of this clinical trial. Subjects treated with the MicroStent® will be given an identification card used to alert health care providers that they have an implanted metal device. Investigators who perform the procedure will know which subjects received which treatment. Ultrasound technicians and core lab personnel will be able to visualize the MicroStent® (or absence of the stent) on ultrasound images.

Randomization: Subjects will be randomized after successful crossing of the target lesion and will be considered enrolled in the study subsequent to randomization. A 2:1 randomization ratio will be utilized to randomize 2 subjects to the MicroStent® arm for every 1 subject randomized to the PTA arm. Permuted blocks will be used to maintain a 2:1 ratio across all study sites.

Other Controls for Bias: The primary study endpoints include objective outcomes such as ultrasound measurement of blood flow in the target lesion and the presence or absence of certain clinical procedures involving the target limb during follow-up. Ultrasound measurements and determination of occlusion will be made by an independent core lab, while any clinical procedures qualifying as an endpoint event will be independently adjudicated by

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the CEC to determine the appropriateness of the intervention and the involvement of the target lesion.

9.2. General Statistical Considerations

Data that are of a continuous nature, such as age and vessel diameter, will be summarized by the mean, median, standard deviation, minimum and maximum. The number of observations upon which these statistics are computed will also be presented. Data that are categorical, such as gender and race, will be summarized as frequencies and percentages and include n/N where n is the number of observations in the category and N is the total number of observations across all categories. Percentages will be rounded to the nearest whole percentage.

The significance of differences between independent groups, such as treatment arm, involving continuous data will be tested using Wilcoxon's rank sum test. The difference between medians for each group, along with a 95% bootstrap confidence interval for the difference between medians, will be provided. Analysis of categorical data involving 2 x 2 tables will utilize Fisher's exact test to evaluate the significance of differences. Pearson's chi-square test will be used for tables larger than 2 x 2. Unless otherwise stated, 2-sided tests will be performed and p-values < 0.05 will indicate statistically significant differences. Survival analyses (i.e. Kaplan-Meier) may be conducted as a sensitivity analysis for all proportion based assessments where follow-up may be censored.

The primary effectiveness and safety hypotheses will be tested using the intent-to-treat (ITT) population of study subjects. Subjects will be grouped for comparison according to the treatment to which they were randomized, regardless of the actual treatment received. The robustness of the primary endpoints will also be evaluated using data from the as treated (AT) population, in which subjects will be grouped for comparison according to the treatment they actually received.

The robustness of study results will also be evaluated using the per protocol (PP) population of all subjects who complete the study without major protocol violations. The PP population differs from the ITT in that subjects with major protocol deviations will be excluded from the PP analysis. The reasons for not being included in the PP population will be reported.

The study will be considered successful if the primary effectiveness and safety endpoints are met.

Determination	Who	Timepoint
Lesion occlusion	Core lab	Follow-up
Event relatedness	Principal Investigator	All timepoints
Clinically Driven TLR	CEC	All timepoints
MALE	CEC	All timepoints
Event expectedness	CEC	All timepoints
Bailout procedure	CEC	Index procedure
Ischemic leg/foot ulcers	wound camera	All timepoints

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9.3. Missing Data

Primary and secondary effectiveness endpoint data will be analyzed utilizing the ITT population. Neither baseline nor 6-month follow-up data will be imputed for any subjects with missing data. In general, subjects missing 6-month data will be excluded from the analysis.

The ITT population analysis will be used to judge whether the primary effectiveness objective of primary patency at 6 months has been met. This analysis population will also be used for the sensitivity analysis addressing the robustness of study results. Subjects who do not have a 6-month visit or do not have analyzable DUS data for all treated lesions will be included in the ITT analysis only if they were known to have had a clinically driven TLR prior to 6 months; they will be considered a primary patency failure.

Although every effort will be made to ensure subjects return for each follow-up visit and all required tests are completed, there will be instances when visits are missed, or test results are not available. The primary endpoint is primary patency defined as freedom from occlusion and no clinically driven TLR at 6 months. This endpoint requires two pieces of information; assessment of blood flow and whether the lesion is occluded based on DUS examination and confirmation that the subject did or did not have one or more clinically driven TLR at any time prior to or at the 6-month visit. Subjects who miss the 6-month visit will not have either blood flow nor data pertaining to interventions performed on the target lesion (unless they had an intervention reported prior to 6 months) Subjects who complete the 6-month visit may have data pertaining to whether interventions of the target lesion occurred, but missing blood flow data because of difficulties with the ultrasound examination or the inability of the core lab to determine whether or not the lesion was occluded. For subjects who do not have a clinically-driven TLR within 6 months and for whom the 6-month DUS assessment of occlusion is missing, will have outcome imputed as free from occlusion if the next available DUS examination assessment post-6 months confirms freedom from occlusion and no TLR was performed prior to the assessment.

Comparisons of subjects in the MicroStent® arm and those in the PTA arm will be performed using four different methods of dealing with missing data. The results will be presented along with the ITT analysis of primary patency at 6 months in a sensitivity analysis of the robustness of study results.

Imputing Missing Data Using Data From Subsequent Visits Plus Multiple Imputation: For subjects with missing outcome data, despite inclusion of data from subsequent visits, multiple imputation will be performed to impute potential outcomes. Subject factors such as the presence of concomitant coronary artery disease (CAD), diabetes mellitus, baseline Rutherford category, and renal failure status will be used to impute TLR and occlusion separately using propensity score multiple imputation and patency will be derived from the TLR and occlusion imputations. Imputations will be performed separately for each study arm. The difference between arms in the 6-month primary patency proportion will be estimated using Rubin's method for combining inferences across imputations. This analysis will be considered the primary missing data analysis and will help inform which scenarios in the tipping point analysis below are most consistent with the observed data, under the assumption that missing data is missing at random.

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Imputing Missing Data as Failures: A third method of dealing with missing data will be to assume that all subjects with missing primary patency data at 6 months are primary patency failures.

Imputing Missing Data as Successes: A fourth method of dealing with missing data will be to assume that all subjects with missing primary patency data at 6 months are primary patency successes.

Tipping Point Analysis: A tipping point analysis will be employed when analyzing both the primary effectiveness endpoint and the primary safety endpoint, evaluating the range of potential outcomes for missing data from treating all missing data as failures to treating all missing data as successes.

9.4. Subgroup Analyses

Assessment of the effects of a number of background and treatment variables on the primary safety and effectiveness endpoints months will be conducted. These variables include:

- Age (≤ 80 / > 80)
- Age (≤ 65 / > 65)
- Gender (Male / Female)
- Race (Caucasian, African American, Hispanic, Asian, Other)
- BMI (Normal / Overweight / Obese)
- Current smoking status (Smoker / Non-smoker)
- Rutherford classification at the time of enrollment (4, 5)
- Artery segment treated

The effect of each subgroup will be evaluated with a logistic regression model with fixed effects for treatment, subgroup, and treatment-subgroup interaction. These analyses are intended to demonstrate consistency of the treatment effect across subgroups. If the p-value of the treatment-by-subgroup interaction is less than 0.15, additional analyses will be conducted to understand any potential variations by subgroup.

9.5. Primary Effectiveness Endpoint

Primary Effectiveness Endpoint: Primary patency defined as freedom from target lesion occlusion with no clinically driven target lesion reintervention (TLR) , or major amputation at 6 months. It is hypothesized that the proportion of subjects with primary patency at 6 months will be higher among subjects in the MicroStent® arm than subjects in the PTA arm. In statistical terms the null (H_0) and alternative (H_A) hypotheses are:

H_0: $p_{MS} \leq p_{PTA}$

H_A: $p_{MS} > p_{PTA}$

Where: p_{MS} is the proportion of subjects in the MicroStent® arm demonstrating primary patency at 6 months and p_{PTA} is the proportion of subjects in the PTA arm demonstrating primary patency at 6 months.

The proportion of subjects in the MicroStent® arm who demonstrate primary patency at 6 months will be compared to the proportion of subjects in the PTA arm who demonstrate primary patency at 6 months using Fisher's exact test. If the 1-sided p-value associated with

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this test is < 0.025 and the proportion of subjects with primary patency in all lesions in the MicroStent® arm is higher than the proportion for subjects in the PTA arm, the null hypothesis will be rejected in favor of the alternative hypothesis and the effectiveness of the MicroStent® System in achieving primary patency will be demonstrated. Proportions and their 2-sided 95% exact binomial confidence intervals will also be reported.

Primary patency may be lost during the index procedure to treat the target lesion if a bailout procedure is required to obtain a clinically acceptable result. The CEC will review all bailout procedures to verify they were appropriate per the criteria listed in Section 6.2.2. The determination of patency at follow-up will be based upon review of DUS images/videos provided to the core lab by study sites. Study sites will use a common protocol for the DUS examination. The core lab will determine whether or not the target lesion is occluded. Clinically driven TLR is defined as any clinically driven intervention involving the target lesion after the index procedure that is performed to increase blood flow through the lesion. The term TLR includes surgical bypass, thrombectomy, thrombolysis, PTA and/or stenting or other surgical or endovascular procedures to increase blood flow through the target lesion. A TLR is clinically driven if the reintervention procedure was associated with symptoms including complaints of continuing/worsening leg pain, progression/nonhealing limb ulcer, development of a new ulcer with or without the presence of an abnormal test result. Reintervention procedures performed solely because follow-up assessment suggested restenosis in the absence of worsening symptoms will not be categorized as a clinically driven TLR. The determination of whether a reintervention was clinically driven will be made by the CEC. Major amputation is defined as amputation above the level of the ankle joint.

If the core lab determines that the lesion is not occluded at follow-up, no clinically driven TLR, or major amputation has occurred, and no bailout procedure was required during the initial treatment of the target lesion, the lesion will be categorized a primary patency success. If the core lab determines that the lesion is occluded, a clinically driven TLR, or major amputation was performed following the index procedure, or a bailout procedure was required during the initial treatment of the target lesion, the lesion will be categorized a primary patency failure. Determination, responsibility, and timepoint as outlined above is summarized in Section 9.2.

The analysis of primary patency data will be based on the ITT population with known data pertaining to occlusion and the occurrence of clinically driven TLR, or major amputation or bailout procedure for all treated lesions within 6 months. Subjects who exit the study prematurely will be excluded, unless they had a bailout procedure, clinically driven TLR, major amputation, or occlusion of a treated lesion prior to exiting the study, in which case they will be counted as primary patency failures.

An additional, supportive analysis of the primary effectiveness endpoint will be performed considering only device-related occlusion and device related clinically-driven TLR as failures of the endpoint.

Justification Of Sample Size: Sample size requirements were based on the assumption that patency rates for the proposed clinical trial will be similar to those reported in the literature. It was assumed that at 6 months, 82% of subjects in the MicroStent® arm will demonstrate primary patency and 60% of PTA arm subjects will demonstrate primary patency. A total of 165 subjects (110 MicroStent® System and 55 PTA) is required to achieve 80% power to detect

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the difference using a 1-sided Fisher's exact test with alpha of 0.025. A 2 to 1 randomization scheme will be used for this study in which 2 subjects will be randomized to the MicroStent® System arm for each subject randomized to PTA. An additional 12 subjects will be enrolled and randomized to allow for up to 7.5% premature exit from the study. In addition, 15 subjects were enrolled as part of the initial, non-randomized phase of the study. These subjects will not be included in the primary endpoint analysis. They will, however, undergo all follow-up visits and their data will be reported separately. Thus, a total of 192 subjects may be enrolled in the study.

9.6. Hypothesis Tested Secondary Effectiveness Endpoints

There are two secondary effectiveness endpoints with hypotheses to be tested. The first is freedom from major amputation (above the ankle) at 6 months post index intervention. The second is reduction in size of leg/foot ulcers at 6 months post index intervention. Hypothesis testing of these secondary endpoints will be conducted only after both primary endpoints have been met in order to preserve the overall Type I error rate.

The Hochberg method will be used to control the family wise error rate. This method involves rank ordering the two observed p-values from highest to lowest. If the highest p-value is < 0.025, the null hypotheses for each secondary effectiveness endpoint will be rejected in favor of the alternative hypotheses and the effectiveness of the MicroStent® System will be supported for both secondary endpoints. If, however, the highest p-value is ≥ 0.025, the null hypothesis for the associated secondary endpoint will not be rejected and the critical value for the second endpoint will be adjusted by dividing 0.05 in half or 0.025. If the next highest p-value is < 0.0125, the null hypothesis will be rejected in favor of the alternative. But if both observed p-values are ≥ 0.0125 then neither secondary endpoint null hypothesis will be rejected and the effectiveness of the MicroStent® System will not be supported for either secondary endpoint.

Secondary Effectiveness Endpoint #1: Freedom from major amputation (above the ankle) at 6 months post index intervention.

It is hypothesized that the proportion of subjects without major amputation at 6 months will be higher among subjects in the MicroStent® arm than subjects in the PTA arm. In statistical terms the null (H_0) and alternative (H_A) hypotheses are:

H_0: $p_{MS} \leq p_{PTA}$

H_A: $p_{MS} > p_{PTA}$

Where: p_{MS} is the proportion of subjects in the MicroStent® arm without major amputation at 6 months and p_{PTA} is the proportion of subjects in the PTA arm without major amputation at 6 months.

The proportion of subjects in the MicroStent® arm who have not undergone major amputation 6 months will be compared to the proportion of subjects in the PTA arm who have not undergone major amputation at 6 months using Fisher's exact test. If the 1-sided p-value of this test is less than or equal to the Hochberg-adjusted critical value and the proportion of subjects in the MicroStent® arm without major amputation is higher than the proportion for

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subjects in the PTA arm, the null hypothesis will be rejected in favor of the alternative hypothesis and the effectiveness of the MicroStent® System in preventing major amputations will be demonstrated. Proportions and their 2-sided 95% exact binomial confidence intervals will also be reported.

In addition, time until major amputation will be analyzed using the Kaplan-Meier method. Survival time will be computed as the number of days between index treatment and 1) last study contact including date of withdrawal or exit including death or 2) date of major amputation whichever occurs first. Major amputation will be regarded as a terminal event. Cumulative survival rates through 6 months will be displayed graphically for each treatment arm separately. The significance of differences between the two treatment arms will be tested using the log rank test.

Secondary Effectiveness Endpoint #2: Reduction in size of leg/foot ulcers at 6 months post index intervention.

The area (mm^2) of leg/foot ulcers distal to arterial lesions will be measured using specialized wound cameras during physical examination prior to treatment and at each follow-up visit. These cameras measure and calculate the area of wounds automatically. Wound size change scores will be computed by subtracting measurements at baseline from those obtained at follow-up such that negative scores indicate a reduction in wound size and positive scores indicate an increase. It is expected that, on average, subjects in the MicroStent® arm will demonstrate greater reduction in wound size at 6 months than subjects in the PTA arm. In statistical terms the null (H_0) and alternative (H_A) hypotheses are:

H_0: $\mu_{MS} \geq \mu_{PTA}$

H_A: $\mu_{MS} < \mu_{PTA}$

Where: μ_{MS} is the mean wound size change score of subjects in the MicroStent® arm at 6 months and μ_{PTA} is the mean change score of subjects in the PTA arm at 6 months.

Change score summary statistics including the mean and standard deviation will be computed and presented for each treatment arm separately. Wound size change scores among subjects in the MicroStent® arm will be compared to change scores among subjects in the PTA arm using a Wilcoxon rank sum test. If the 1-sided p-value of this test is less than the Hochberg-adjusted critical value and the mean change score for the MicroStent® arm is less than the mean change score for subjects in the PTA arm, the null hypothesis will be rejected in favor of the alternative hypothesis and the effectiveness of the MicroStent® System in reducing leg/foot ulcers will be demonstrated.

This analysis will include only subjects presenting with leg/foot ulcers prior to their index treatment and who complete their 6-month visit.

9.7. Exploratory Secondary Effectiveness Endpoints

Because the following variables are exploratory in nature and statistical inferences will not be included in product labeling, no adjustments will be made for multiple comparisons. For all endpoints including reinterventions or amputations, in addition to the analysis outlined below, the endpoints will also be analyzed considering only device-related events.

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Exploratory Effectiveness Endpoint #1: Freedom from clinically driven TLR at all timepoints.

It is expected that some subjects, after the index procedure, may experience worsening symptoms and require additional intervention or reintervention of lesions treated during the index procedure. Freedom from clinically driven TLR allows for the estimation of the proportion of subjects who did not need any additional intervention or reintervention to maintain patency.

The proportion of subjects in the MicroStent® arm who demonstrate freedom from clinically driven TLR will be compared to the proportion of PTA arm subjects who demonstrate freedom from clinically driven TLR using Fisher's exact test. Proportions and their 2-sided exact binomial confidence intervals will also be reported.

Exploratory Effectiveness Endpoint #2: Freedom from major amputation (above the ankle) at all timepoints post index intervention. The proportion of subjects in the MicroStent® arm who demonstrate freedom from major amputation at each timepoint will be compared to the proportion of PTA arm subjects who demonstrate freedom from major amputation at each timepoint using Fisher's exact test. Proportions and their 2-sided exact binomial confidence intervals will also be reported.

Exploratory Effectiveness Endpoint #3: Reduction in size of ischemic leg/foot ulcers at all timepoints post index intervention.

The area (mm^2) of leg/foot ulcers distal to arterial lesions will be measured using specialized wound cameras during physical examination prior to treatment and at each follow-up visit. These cameras measure and calculate the area of wounds automatically. Wound size change scores will be computed by subtracting measurements at baseline from those obtained at follow-up such that negative scores indicate a reduction in wound size and positive scores indicate an increase.

Change score summary statistics including the mean and standard deviation will be computed and presented for each treatment arm separately. Wound size change scores among subjects in the MicroStent® arm will be compared to change scores among subjects in the PTA arm using a Wilcoxon rank sum test.

Exploratory Effectiveness Endpoint #4: Freedom from clinically driven TVR at all timepoints post index intervention.

It is expected that some subjects, after the index procedure, may experience worsening symptoms and require additional intervention or reintervention of vessels treated during the index procedure. Freedom from target vessel reintervention allows for an estimation of the proportion of subjects who did not need any additional reintervention of the target vessel to maintain patency.

The proportion of subjects in the MicroStent® arm who demonstrate freedom from clinically driven TVR at will be compared to the proportion of PTA arm subjects who demonstrate freedom from device-related clinically driven TVR at each timepoint using Fisher's exact test. Proportions and their 2-sided exact binomial confidence intervals will also be reported.

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Exploratory Endpoint #5: Amputation free survival at all timepoints post index intervention.

Amputation free survival (AFS) is a composite endpoint assessing the number of subjects who have survived to the stated endpoint without experiencing a major (above the ankle) amputation.

The proportion of subjects in the MicroStent® arm who demonstrate AFS will be compared to the proportion of subjects in the PTA arm who demonstrate AFS using Fisher's exact test. Proportions and their 2-sided exact binomial confidence intervals will also be reported.

Exploratory Endpoint #6: Secondary patency defined as freedom from occlusion with or without clinically driven TLR at all timepoints post index intervention.

It is expected that some subjects, after the index procedure, may experience worsening symptoms and require additional reintervention of lesions treated during the index procedure. Secondary patency allows for the estimation of effectiveness at follow-up even if a target lesion required additional reintervention to maintain patency.

The proportion of subjects in the MicroStent® arm who demonstrate secondary patency at each timepoint will be compared to the proportion of PTA arm subjects who demonstrate secondary patency at each timepoint using Fisher's exact test. Proportions and their 2-sided exact binomial confidence intervals will also be reported.

Exploratory *Effectiveness Endpoint* #7: Change in lumen diameter within the lesion immediately post-treatment compared to pre-treatment as measured by angiography.

Lumen diameter will be measured via angiography prior to treatment and post-treatment. Angiography will be conducted using a single protocol developed by the core lab. The core lab will also review all images and estimate lumen diameters for use in this exploratory endpoint analysis.

A difference score will be computed by subtracting pre-treatment diameters from post-treatment values such that positive change scores indicate an increase in diameters while negative change scores will indicate a decrease in lumen diameter.

Change score summary statistics including the mean and standard deviation will be computed and presented for each treatment arm separately. Change scores for lesions in subjects in the MicroStent® arm will be compared to change scores among those in the PTA arm using Wilcoxon's rank sum test.

Exploratory Effectiveness Endpoint #8: PSVR patency defined as peak systolic velocity ratio (PSVR) ≤ 2.4 and no clinically driven TLR at all timepoints post index intervention.

The proportion of subjects in the MicroStent® arm who demonstrate PSVR patency will be compared to the proportion of subjects in the PTA arm who demonstrate PSVR patency using a Fisher's exact test. Proportions and their 2-sided 95% exact binomial confidence intervals will also be reported.

The determination of PSVR patency at follow-up will be based upon review of DUS images/videos provided to the core lab by study sites. Study sites will use a common protocol

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for the DUS examination. A PSVR > 2.4 has been shown to correspond to lesion stenosis of ≥ 50% when compared to angiography (8) with sensitivity of 81% and specificity of 93% for femoropopliteal lesions. If the core lab determines that the lesion is patent (PSVR ≤ 2.4) at follow-up and no clinically driven TLR has occurred, the lesion will be categorized a PSVR patency success. If the core lab determines that the lesion is not patent (PSVR > 2.4) or a clinically driven TLR was performed following the index procedure, the lesion will be categorized a PSVR patency failure.

Exploratory Effectiveness Endpoint #9: Change in health status (measured by the EQ-5D-3L) at follow-up compared to pre-treatment.

The EQ-5D-3L is a questionnaire that measures health status in 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. A single summary index score can be constructed using responses from the 5 dimensions and applying country-specific weights with higher scores indicating better health status. There is also a separate VAS (visual analog scale) score that asks the subject to rate their health status on a vertical line ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). Summary index scores and VAS scores will be analyzed separately.

Difference scores will be computed by subtracting pre-treatment scores from post-treatment values such that positive change scores indicate an increase in health status while negative change scores will indicate a decrease in health status.

Change score summary statistics including the mean and standard deviation will be computed and presented for each treatment arm separately. Change scores for subjects in the MicroStent® arm will be compared to change scores among those in the PTA arm using Wilcoxon's rank sum test.

Exploratory Effectiveness Endpoint #10: Change in daily walking ability at follow-up compared to pre-treatment as measured by the Walking Impairment Questionnaire (WIQ).

The level of walking ability of each subject will be measured at baseline and each follow-up visit utilizing the Walking Impairment Questionnaire (WIQ). The WIQ utilized in this study contains 14 items that contributed to 3 subscales (distance, speed and stair) and an overall score. Participants answer each item on a scale from 0 for "unable to do" to 4 for "no difficulty". Each response is weighted based on the difficulty of the task (e.g., the weight for "walk slowly" is 1.5 whereas for the weight for "run or jog" is 5). Subscale scores are determined by dividing the weighted answers by the maximum possible weighted score and multiplying by 100. Each score ranges from 0–100 with lower scores indicating lower performance. The overall score is the average of all 3 subscores. Items coded as "Didn't Do For Other Reasons" are removed from the denominator of the weighted score to calculate a percent score based on the items that remained.

Difference scores will be computed by subtracting the pre-treatment scores from the post-treatment scores such that positive change scores indicate an increase in walking ability relative to baseline while negative change scores will indicate a reduced walking ability relative to baseline.

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Exploratory Endpoint #11: Change in clinical Rutherford category at follow-up compared to pre-treatment.

The Rutherford category of each subject will be assessed at the baseline visit and each follow-up visit by a clinician. The change in Rutherford category between baseline and follow-up will be represented with the number of subjects who experienced an improvement (decrease; -1, -2, -3 or more), no change (0), or deterioration (increase; +1, +2, +3, clinically driven TLR or amputations) for each arm.

Exploratory Endpoint #12: Change in ABI/TBI at follow-up compared to pre-treatment

The ankle-brachial index will be measured at the baseline visit and each follow-up visit. The mean and 95% confidence interval at baseline will be compared to the mean and 95% confidence interval at each follow-up visit.

9.8. Primary Safety Endpoint

Primary Safety Endpoint: A composite of freedom from perioperative death (POD) at 30-days and freedom from MALE at 6 months.

The definition of MALE includes above the ankle amputation of the index limb and/or major reintervention with involvement of the target lesion (new bypass graft, jump/interposition graft revision, thrombectomy, and/or thrombolysis). Study subjects will be assigned to one of two categories: 1) Those who experience a primary safety event (die within 30 days of their index procedure or experience one or more MALE within 6 months) and 2) those who do not experience a primary safety event. It is expected that the proportion of subjects in the MicroStent® arm who do not experience a primary safety event will not be inferior to the proportion of subjects in the PTA arm who do not undergo such events. In statistical terms the null (H_0) and alternative (H_A) hypotheses are:

H_0: $p_{MS} < p_{PTA} - \delta$

H_A: $p_{MS} \geq p_{PTA} - \delta$

Where: p_{MS} is the proportion of subjects in the MicroStent® arm who did not experience a primary safety event, p_{PTA} is the proportion of subjects in the PTA arm who did not experience a primary safety event and δ is a noninferiority margin of 0.1 (10%).

This analysis will not include subjects who were lost to follow-up or exited the study prior to 6 months, unless they experienced one or more primary safety event prior to exiting the study, in which case they will be included as a failure.

The hypothesis will be tested using a one-sided Farrington and Manning test. If the p-value associated with the test statistic is < 0.025, the null hypothesis will be rejected in favor of the alternative hypothesis and the safety of the MicroStent® System will be demonstrated.

Secondary supportive analysis of the primary safety endpoint will be performed considering only device-related events.

Justification Of Sample Size: Rocha-Singh et al. (9) reported that 8.4% (9/107) of subjects treated for CLI with a self-expanding stent had major amputations within 6 months following treatment (n=8) or died within 30 days (POD) (n=1). In a meta-analysis of patients treated for

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CLI using PTA, Mustapha et al. (10) estimated a 1-year amputation rate of 14.9% based on the results of 37 studies. Assuming the 6-month rate to be half the 1-year rate suggests a 7.45% amputation rate at 6 months. The meta-analysis did not include POD as an endpoint. Thus, it appears appropriate to assume that the 6-month major amputation + POD rate for both the MicroStent® arm and PTA arm is approximately 8%. Given that both of the referenced studies included Rutherford 6 subjects and a minimal number of Rutherford 3, it is reasonable to assume that the rates of MALE + POD events in the proposed study (Rutherford 4-5) will be lower because enrolled subjects will be healthier than those reported in the literature. Thus, sample size requirements were based on the assumption that the MALE + POD rates are approximately 5% for both treatment groups. For a noninferiority margin of 10%, a total of 161 subjects (107 MicroStent® System and 54 PTA only) is required to achieve 80% power with alpha of 0.025.

9.9. Secondary Safety Endpoints

Secondary Safety Endpoint #1: Freedom from major adverse limb events (MALE) at all timepoints. The number and percentage of subjects who did not experience MALE will be presented for both treatment arms separately.

The remaining secondary safety endpoint utilizes data collected on adverse events that occur throughout the course of the study. The intent is to construct a safety profile for the MicroStent® System. Device and procedure relatedness will be according to the Principal Investigator.

Secondary Safety Endpoint # 2: Frequency and severity of serious adverse events and device and procedure-related adverse events at any time during the study. The frequency and severity of serious adverse events and adverse events judged to be device and/or procedure-related will be summarized for subjects treated with the MicroStent® System separately from those that occur among subjects treated with PTA only. Similar events will be categorized and the frequency of events, number of subjects who experience them along with severity will be tabulated. In addition, detailed patient lists of each serious adverse events and device and/or procedure-related adverse event will be provided and include a description of the event, severity, duration, treatment for the event and outcome.

9.10. Treatment Procedure Data

Treatment data will be collected and reported for both the MicroStent® arm and PTA arm. Data to be reported includes the number of times each device size is used, number of procedures per subject, number of times difficulties with either the device or procedure are encountered, and any procedure-related or device-related adverse events. Any procedures performed subsequent to the index procedure will include reason for the procedure, type of procedure (PTA, Stent, bypass, etc.) and whether it is performed on a lesion previously treated during the study.

9.11. Poolability of Data from Different Study Sites

Data will be analyzed to evaluate whether data from the various study sites can be pooled. Results will be reported separately for each site regardless of the number of subjects enrolled. Study sites with 5 or more enrolled subjects will be treated as individual sites whereas those with fewer than 5 subjects will be pooled into ‘super sites’ according to their geographical

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closeness so that the combined super sites would have 5 or more subjects. Once sufficient sites have been pooled to create a super site with 5 or more subjects, pooling for that super site will stop and pooling for another super site will begin. If the remaining site with less than 5 subjects are not able to be pooled to create a super site, they will be added to previous super sites according to geographical closeness. The variables to be tested include:

- The primary effectiveness endpoint, primary patency at 6 months
- The primary safety endpoint, freedom from POD at 30 days and MALE at 6 months

Heterogeneity among study sites in the estimated treatment effect on each outcome will be tested using the interaction between randomized arm and site in a logistic regression with the primary endpoint as a binary outcome. If the 2-sided p-value associated with the interaction test is < 0.15, the variable will be deemed to vary significantly between study sites.

9.12. Protocol Deviations

Protocol deviations will be classified as to whether they are related to:

- Inclusion/exclusion criteria
- Informed consent
- MicroStent® System use
- Assessments not done or done outside window
- Follow-up procedures not done as specified in the protocol
- Study interventional procedures not performed as specified in the protocol or device labeling
- Deviations to randomization assignment
- Events not reported per protocol
- Other

The deviations will be reviewed as to whether they affect the scientific integrity of the study in defining the per protocol population.

Protocol deviations will be reported by the investigational sites in the electronic database. Frequencies of protocol deviations will be presented for each category and for each treatment group separately. In addition, complete listings of protocol deviations will be provided.

10.0. Data Management and Monitoring

10.1. Study Data Collection

Electronic Case Report Forms (eCRF) will be used to capture data for the safety and performance analysis. Sites will be required to maintain source documentation, in accordance with GCP guidelines and 21 CFR 812 to substantiate all data collected.

10.2. Site Data Monitoring and Quality Control

Primary data collection based on source-documented hospital chart reviews will be performed by the clinical research team, which may include sponsor or sponsor's designees. As a performance target, eCRFs will be completed within 14 days of the procedure or scheduled visit. The sponsor will provide adequate source document worksheets for capture of study-specific data during the procedure and follow-up visits that may not normally be collected during routine procedures.

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The clinical site will be monitored periodically by the sponsor's personnel, or sponsor's designee, for protocol adherence, accuracy of eCRFs, and compliance to applicable regulations. Any observations of non-compliance will be reviewed with the Principal Investigator. Any evident pattern of ongoing non-compliance may result in corrective actions by the sponsor, including potential study suspension, as deemed appropriate by the sponsor.

The sponsor will review significant new information, including unanticipated serious adverse events and ensure that such information is provided to the appropriate regulatory agencies, the investigators and to all reviewing IRBs as required by applicable regulations.

11.0. Safety Oversight

11.1. Safety: Complication Analysis and Acceptance

Revascularization catheter procedures are known to have inherent risks of complications. No new or additional complications or adverse events are expected due to the MicroStent® portion of the procedure.

11.2. Clinical Events Committee (CEC)

A Clinical Events Committee (CEC) will be formed to review and adjudicate all endpoint events as listed below. The CEC will consist of at least three (3) physicians with experience in surgical and/or endovascular treatment of CLI patients, who are independent from the Sponsor and are not investigators in the study. Specific roles, responsibilities and processes will be described in a CEC Charter which will be agreed upon by CEC members and published prior to commencement of enrollment.

Outcomes Adjudication: Reports of endpoint events will be reviewed and adjudicated, including but not limited to:

- Major index limb amputation
- Death
- Major and minor reintervention of the index limb, including determination of whether the re-intervention was clinically driven

Adjudication may also include, but is not limited to, determination of expectedness of the event for SADEs and procedure-related SAEs.

Appropriateness of Bailout Procedure: The CEC will review procedural angiograms and/or procedure notes and determine the appropriateness of any bailout procedures per the criteria described in Section 6.2.2.

11.3. Data and Safety Monitoring Board (DSMB)

An Data and Safety Monitoring Board (DSMB) DSMB will be formed to review data from the clinical investigation to evaluate the safety and effectiveness of the investigational device. The DSMB will be formed prior to subject enrollment and the names, affiliations, and academic backgrounds of all members will be provided to the regulatory authorities as required by local regulation.

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The members of the DSMB are responsible for safeguarding the rights and welfare of study participants, assessing the safety and effectiveness of study procedures, and reviewing the overall conduct of the clinical investigation. The DSMB will regularly review clinical investigation data to evaluate study conduct, investigational device safety, and scientific validity and integrity of the investigation. Study thresholds and associated stopping rules will be included in the DSMB charter.

The DSMB will provide recommendations regarding the implementation and progress of clinical investigation, including continuation, suspension and/or termination of the clinical investigation. Specific roles, responsibilities and processes will be described in an DSMB Charter which will be agreed upon by DSMB members and published prior to commencement of enrollment.

11.4. Study Termination

If MMS and/or the DSMB and/or Study Principal Investigator determine that an event, or event rate presents an unreasonable risk to subjects, then the investigation or parts of the investigation presenting that risk shall be immediately revised or terminated. Termination shall occur no later than 5 working days after the sponsor makes this determination and no later than 15 working days after the sponsor first received notice of the event or the event rate. MMS will notify all participating investigators, IRBs, and the FDA of the termination of the investigation.

12.0. Quality Control and Quality Assurance

12.1. Site Training

To ensure accurate, complete, and reliable data, the Sponsor or its representative will provide instructional material to the study site, as appropriate:

- Instruct the investigators and study personnel on the protocol, the completion of the eCRFs, and study procedures.
- Communicate regularly with site personnel via mail, email, telephone, and/or fax.
- Make periodic visits to the study site.

12.2. Physician Training

All investigators participating in this clinical trial are skilled in vascular interventional procedures and the use of endovascular catheters. The Site Initiation Visit will include procedurally relevant workflow and instruction for the MicroStent® System.

12.3. Audits and Inspections

The Principal Investigator for the site will also allow representatives of the governing IRB, the United States Food and Drug Administration (FDA), and other applicable regulatory agencies to inspect all study records, eCRFs, and corresponding portions of the subject's office and/or hospital medical records at regular intervals throughout the study. These inspections are for the purpose of verifying adherence to the protocol, completeness and exactness of the data being transcribed into the eCRF, and compliance with FDA or other regulatory agency regulations.

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The Principal Investigator for the site will inform the sponsor or sponsor's designee in advance if they are to be audited or inspected by any regulatory agencies. The sponsor will also inform the site if they are made aware of a pending audit or inspection by a regulatory agency.

12.4. CEC and DSMB Member Training

All CEC and DSMB members will review the protocol, the procedure/device, the committee Charter, and the documentation requirements prior to commencement of duties for this trial.

13.0. Ethical Considerations

13.1. Trial Conduct

The study will be performed in accordance with the relevant parts of Title 21 CFR Parts 812, 50, 54, and 56, and the ICH Guidelines for Good Clinical Practices (E6).

13.2. Institutional Review Board (IRB)

A copy of the protocol, proposed Informed Consent form, other written patient information, and any proposed advertising material must be submitted to the Institutional Review Board (IRB) for written approval prior to use. A copy of the written IRB approval of the protocol and Informed Consent form must be received by the sponsor before recruitment of patients into the study and shipment of investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB as well as any required regulatory agencies, for all subsequent significant protocol amendments and significant changes to the Informed Consent form. The investigator should notify the IRB of deviations from the protocol or SAEs and UADEs occurring at the site and other SAE/UADE reports received from the sponsor in accordance with local procedures.

The investigator will be responsible for obtaining annual IRB approval and renewal throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be sent to the sponsor.

13.3. Provisions for Maintaining Confidentiality

Confidentiality of subjects will be maintained throughout the study. A unique identification code will be assigned to each subject participating in this study. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity. The Sponsor and their CRO representative will make every reasonable effort to protect the confidentiality of the subjects participating in the study.

13.4. Provisions for Compensation in Case of Injury

On the conditions that a subject follows the directions of the study investigators in charge of this study, and in a case a subject is physically injured due to the trial procedure given under the plan for this study, the sponsor will pay the medical expenses for the treatment of that injury.

The sponsor will not provide payment for management of the normally expected consequences of the treatment of a subject. Subjects will not be compensated for

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participating in the study. Modest reimbursement for travel costs related to attendance of follow-up visits may be granted if approved by the responsible IRB.

By signing the Informed Consent Form, a subject will not waive any of his/her legal rights or release the parties involved in this study from liability for negligence.

13.5. Emergency Actions

The sponsor accepts the right of the investigator to deviate from the protocol in an emergency when necessary to safeguard the life or the physical well-being of a study subject. The investigator must give notice of any emergency deviations and justification for the deviation to the sponsor and the IRB as quickly as possible after the episode, in any event no later than 24 hours after the emergency.

13.6. Informed Consent Form

A sample Informed Consent form is provided in Attachment 1 for the investigator to prepare for use at his/her site. The written Informed Consent documents should be prepared in the language(s) of the potential patient population at a reading level that the subjects can understand.

The reviewing IRB and the sponsor must first approve the Informed Consent forms that are used. The Informed Consent forms that are used should be in accordance with the current guidelines as outlined by the relevant parts of Title 21 CFR Parts 812, 50, 54, and 56, and the ICH Guidelines for Good Clinical Practices (E6).

Prior to participation in the clinical study, each patient must give written Informed Consent after the context of the study has been fully explained to the patient in language that is easily understood by the patient. The patients must also be given the opportunity to ask questions and have those questions answered to their satisfaction.

Written Informed Consent must be recorded appropriately by means of the patient's, or their legal representative's dated signature. The patient will receive a copy of the signed Informed Consent form.

14.0. Study Administration

The sponsor will make necessary efforts to ensure that this study is conducted in compliance with GCPs and all applicable regulatory requirements.

14.1. Source Documentation

The principal investigator must maintain detailed source documents on all study subjects who are enrolled in the study. Source documents include subject medical records, hospital charts, clinic charts, investigator's subject study files, as well as the results of diagnostic tests (e.g., laboratory tests).

The following minimum information should be recorded in the subject's medical records:

- The date the subject entered the study and the subject number
- The study protocol number and the name of the Sponsor

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- The date that informed consent was obtained and a statement of informed consent process
- Evidence that the subject meets study eligibility requirements (e.g., medical history, study procedures and/or evaluations)
- The dates of all study related subject visits
- Evidence that required procedures and/or evaluations were completed, including required photographs, angiographic images, and DUS images
- Use of any concurrent cardiovascular medications
- Documentation of specific device used, if any
- Occurrence and status of any Adverse Events
- The date the subject exited the study, and a notation as to whether the subject completed the study or was discontinued, including the reason for discontinuation.

14.2. Record Retention

The investigator will maintain all essential study documents and source documentation, in original format, that support the data collected on the study subjects in compliance with the ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product.

14.3. Criteria for Terminating Study

The sponsor reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs, and FDA will be notified in writing in the event of termination (see Section 11.4).

Possible reasons for study termination include:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of the sponsor to suspend or discontinue development of the device.

14.4. Criteria for Suspending/Terminating a Study Center

The sponsor reserves the right to stop the enrollment of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled or if the center has multiple or severe protocol violations without justification or fails to follow remedial actions.

Possible reasons for suspending/terminating a study center include:

- Repeated failure to complete case report forms prior to scheduled monitoring visits
- Failure to obtain written Informed Consent prior to treatment
- Failure to report SAE/UADE to sponsor within 24 hours of knowledge
- Loss of (or unaccounted for) investigational product inventory

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14.5. Amending the Protocol

An investigator may not make protocol changes without prior approval by the sponsor. All significant protocol changes that may affect the following must be submitted and approved by the IRB before initiating the change:

- validity of the data or information resulting from the completion of the approved protocol;
- relationship of the likely subject risk to benefit relied upon to approve the protocol;
- scientific soundness of the investigational plan, or;
- rights, safety, or welfare of the human subjects involved in the investigation.

The sponsor will submit a copy of any protocol amendment to the investigators for their IRB to review and ensure the study continues to be conducted consistently across all sites. The investigative site must send sponsor a copy of the IRB approval letter for the protocol amendment.

The sponsor may make certain administrative changes to the protocol without prior approval of the IRB and will notify all investigative sites of such changes to ensure the study continues to be conducted accordingly.

14.6. Publication Policy

The existence of this clinical study is confidential, and it should not be discussed with persons outside of the study. Additionally, the information in this document and regarding this study contains trade secrets and commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by regional or national law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, but all such persons must be instructed not to further disseminate this information to others. These restrictions of disclosure will apply equally to all future information provided that is indicated as confidential.

The data generated by this clinical study are the property of the sponsor and should not be disclosed without their prior written permission. These data may be used by the sponsor now and in the future for presentation or publication at sponsor's discretion or for submission to governmental regulatory agencies. The principal investigator may publish or present the study results with prior consent of the sponsor but will not disclose confidential information. Prior to submission by a principal investigator for publication or presentation, the sponsor will be provided with the opportunity to review the submission for confidential information and accuracy.

15.0. Regulatory Considerations

15.1. Sponsor's Responsibilities

The sponsor of this clinical study has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the United States Food and Drug Administration (US FDA). Together, both the sponsor and its designees will ensure adherence to the sponsor's general duties, selection of investigators, monitoring, supplemental applications, maintaining records, and submitting reports.

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The sponsor's general duties consist of obtaining IRB approval prior to shipping the devices, selecting qualified investigators and shipping devices only to those qualified investigators. The sponsor is also required to obtain signed study agreements, to provide the investigators with the information necessary to conduct the study and adequate on-site training to conduct the study, to ensure proper clinical site monitoring, and to provide the required reports to the investigators, IRBs and appropriate regulatory agencies.

The sponsor will be responsible for providing quality data that satisfies appropriate regulations and informing of serious unanticipated adverse events and deviations from the protocol. Written progress reports and a final report will be prepared.

15.1.1. Investigational Device Distribution

MMS will control the distribution of the investigational devices. The investigator is responsible for ensuring that the devices are ordered for shipment to arrive at the hospital before the procedure date.

Devices will be shipped with an Investigational Device Shipment Record. This form is to be used by MMS and the investigational site to record any shipments of the investigational device. A copy is to be retained by the shipper and the recipient.

15.2. Investigator Responsibilities

15.2.1. Investigator Agreement

The investigator must:

- Agree to sign and adhere to the Investigator Agreement
- Be willing to provide required assessments for analysis
- Be willing to perform and be capable of performing treatment procedures as outlined in this protocol
- Comply with all required elements of this protocol (e.g., perform testing and follow-up as specified, especially during personnel transitions) and supply material suitable for quantitative analysis
- Agree to obtain written Informed Consent before any study specific procedures are performed in accordance with GCP
- Complete all case report forms prior to scheduled monitoring visits
- Be willing to change hospital routine if required by protocol (as long as subject safety and well-being is not compromised).

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15.2.2. Required Reports

Table 5 displays a list of the reports that are the principal investigator's responsibility to generate. The local IRB may have additional reporting requirements.

Table 5: Reports Required from Clinical Investigators

Type of Report	Prepared By Investigator For:	Time Constraints of Notification
Subject death during investigation	Sponsor	Within 24 hours of knowledge of event
Unanticipated adverse device effect	Sponsor	If serious or life-threatening, within 24 hours; otherwise within 10 working days
Subject withdrawal	Sponsor	Within 5 working days of withdrawal
Withdrawal of IRB or Ethics Committee approval	Sponsor	Within 5 working days of withdrawal
Deviations from investigational plan (emergent)	Sponsor	Within 5 working days of the site becoming aware of the deviation
Informed consent not obtained	Sponsor	Within 5 working days of date of deviation
Final summary report	Sponsor	Within 3 months of finalization

15.2.3. Investigational Device Accountability

The investigator shall maintain adequate records of the receipt and disposition of all investigational devices. The investigator is responsible for ensuring that the investigational devices are used only under the investigator's supervision and are only used according to this protocol and any approved amendments. The investigator will not supply an investigational device to any person not authorized to participate in the study. The investigator shall document in the operative notes and CRF's the lot number of the devices used during a case. In addition, the investigator shall keep complete and accurate records of all devices used or unused that have been returned to MMS in a Device Accountability Log provided by the sponsor.

After the cases are completed, all unused devices must be accounted for and shipped back to MMS. Instructions for device return to MMS will be reviewed at the site initiation visit.

IMPORTANT: Please note that the devices must be labeled with a "BIOHAZARD" sticker if there is reasonable belief that the device has come in contact with blood or infectious substances that are known or are believed to cause disease in animals or humans.

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16.0. Glossary of Terms

ACRONYMS used throughout the protocol:

Acronym	Definition
ABI	Ankle brachial index
AE	Adverse event
AT	As treated
BMI	Body mass index
BTK	Below the knee
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CLI	Critical limb ischemia
CRF	Case report form
CT	Computed tomography
DUS	Duplex Ultrasound
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good clinical practice
ICF	Informed consent form
ICH	International Council for Harmonization
DSMB	Data and Safety Monitoring Board
IFU	Instructions for use
IRB	Internal review board
ITT	Intent-to-treat
MALE	Major adverse limb event
MMS	Micro Medical Solutions, Inc.
PAD	Peripheral arterial disease
POA	Power of Attorney
POD	Perioperative Death
PP	Per protocol
PSVR	Peak systolic velocity ratio
PTA	Percutaneous transluminal angioplasty
RVD	Reference vessel diameter
SAE	Serious adverse event
SFA	Superficial femoral artery
TBI	Toe brachial index
TLR	Target lesion reintervention
TVR	Target vessel reintervention
UADE	Unexpected adverse device effect
WIQ	Walking Impairment Questionnaire

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ALL-CAUSE DEATH, divided into 2 categories:

- *Cardiac death* is defined as death due to any of the following:
  1. Acute myocardial infarction.
  2. Sudden cardiac deah.
  3. Death due to heart failure.
  4. Death due to stroke.
  5. Death due to cardiovascular procedures.
  6. Death due to cardiovascular hemorrhage.
  7. Death due to other cardiovascular causes.

- *Non-cardiac death* is defined as any death with a specific cause that is not thought to be cardiovascular in nature.
- *Undetermined is any death not attributable to one of the above categories of cardiovascular death or to a specific non-cardiovascular cause.*

AMPUTATION

- *Major amputation* is defined as amputation of the index limb at the level above the ankle.

- *Minor amputation* is defined as amputation(s) of the index limb/metatarsals at the level below the ankle. Indication for minor amputations should be documented in the CRF.

- *Pre-planned amputation* is defined as minor amputation(s) that are prospectively anticipated as part of the overall procedure and care plan for a subject. These anticipated procedures should be documented in the medical record prior to the index procedure.

AMPUTATION FREE SURVIVAL

A composite of survival without experiencing a major (above the ankle) amputation.

ACUTE TARGET LESION THROMBOSIS REQUIRING IMMEDIATE REPORTING
Identification of thrombus within the target lesion in the acute post-procedural setting, as assessed by duplex ultrasound (DUS) examination or angiogram between 4 – 30 hours post-procedure. Sponsor must be notified within 24 hours of findings.

EMBOLISM
The sudden blocking of an artery by a clot or other material that has been brought to its site of lodgment by the blood current (embolus). Potential sources of emboli include blood clots, fat globules, air bubbles, tissue, clumps of bacteria, thrombus or foreign material.

HEMATOMA
A localized collection of extravasated blood in subcutaneous tissue, usually clotted. A metric ruler should be used to measure the widest portion of the hematoma.

INTIMAL TEAR / DISSECTION

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Disruption of an arterial wall resulting in splitting and separation of the intimal (subintimal) layers. Dissections can be classified by the following grading system:

- *Grade A*: minor radiolucent areas in the lumen without impairment of flow or persistent dye staining after contrast runoff.
- *Grade B*: luminal flap that is radiolucent and runs parallel to the vessel wall with contrast injection but without impairment of flow or persistent dye staining after contrast runoff.
- *Grade C*: contrast appears outside of the vessel lumen as an "extraluminal cap", the staining appears even after contrast clears off the lumen.
- *Grade D*: spiral radiolucent luminal filling defects, often persistent staining after contrast clears from the vessel.
- *Grade E*: new and persistent filling defects in the vessel lumen.
- *Grade F*: lesions that progress to impaired flow or total occlusion

IPSILATERAL DEEP VEIN THROMBOSIS
Presence of a thrombus in the peripheral venous system of the ipsilateral limb. May be a complication of phlebitis or may result from injury to a vein or from prolonged bed rest. Symptoms include a feeling of heaviness, pain, warmth, or swelling in the affected part.

IPSILATERAL LOWER EXTREMITY ARTERIAL EMBOLI
Presence of emboli in the peripheral arterial system of the ipsilateral limb.

LOCALIZED ACCESS SITE INFECTION
Infection occurring at the access site requiring treatment with oral or intramuscular antibiotic therapy. Does not include administration of prophylactic antibiotic regimens.

MAJOR BLEEDING COMPLICATION
Defined as blood loss resulting from the percutaneous revascularization procedure or adjunctive drug therapy requiring transfusions of blood products.

MAJOR ADVERSE LIMB EVENT (MALE)
Consistent with recommendations from Conte et al. (11), events including above the ankle amputation of the index limb and/or major reintervention with involvement of the target lesion (new bypass graft, jump/interposition graft revision, thrombectomy, and/or thrombolysis).

OCCLUSION OF THE TARGET LESION
Absence of flow on color Doppler, and/or absence of flow on angiographic images (conventional or CT).

PERFORATION OF ARTERIAL VESSEL WALL
A hole or break in the arterial wall (e.g., from insertion/advancement of a percutaneous device) as seen on angiography, which may or may not require intervention.

PERI-OPERATIVE DEATH
All-cause death that occurs within the peri-operative period of 30 days post-procedure.

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PSEUDOANEURYSM

A blood vessel abnormality resembling an aneurysm (localized abnormal dilatation of a blood vessel) but consisting of a collection of blood with persistent flow outside an artery, contained by surrounding tissue and due to a leaking hole through all layers of the arterial wall. The leaking hole is due to injury of (e.g., rupture of or trauma to) the arterial wall. The pseudoaneurysm is usually identified by angiography or ultrasound.

RUTHERFORD CLASSIFICATION

Category	Clinical Description
0	Asymptomatic
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Ischemic rest pain
5	Minor tissue loss
6	Major tissue loss

STROKE

A stroke is any sudden development of neurological deficits, such as vertigo, numbness, aphasia, or dysarthria due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm.

SUB-INVESTIGATOR / CO-INVESTIGATOR

Any individual member of the clinical investigation team designated and supervised by the Investigator at an investigational site who performs critical investigation-related procedures and/or makes important investigation-related observations. See also Investigator.

SUBJECT

An individual who participates in a clinical investigation.

TARGET LESION REINTERVENTION

- *Major Reintervention of the Target Lesion* is defined as the creation of a new surgical bypass, the use of thrombectomy or thrombolysis (i.e., procedures done in the setting of lost secondary patency), or major surgical revision such as a jump graft or an interposition graft involving the target lesion.

- *Minor Reintervention of the Target Lesion* is defined as endovascular procedures (PTA, atherectomy, stenting) without thrombectomy / thrombolysis, and minor surgical revisions (patch angioplasty) involving the target lesion.

- *Clinically Driven Target Lesion Reintervention* is defined as procedures performed to address problems that occur as a result of the index procedure and associated with complaints of continued or worsening leg pain, a progressing nonhealing ulcer, or new ulcer formation with or without the presence of an abnormal noninvasive test.

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- *Device-Related Clinically Driven Target Lesion Reintervention* is defined as procedures performed to address problems that occur as a result of the index procedure and that are device-related, and associated with complaints of continued or worsening leg pain, a progressing nonhealing ulcer, or new ulcer formation with or without the presence of an abnormal noninvasive test.

TARGET VESSEL REINTERVENTION

- *Major Reintervention of the Target Vessel* is defined as the creation of a new surgical bypass, the use of thrombectomy or thrombolysis (i.e., procedures done in the setting of lost secondary patency), or major surgical revision such as a jump graft or an interposition graft involving the target vessel.

- *Minor Reintervention of the Target Vessel* is defined as endovascular procedures (PTA, atherectomy, stenting) without thrombectomy / thrombolysis, and minor surgical revisions (patch angioplasty) involving the target vessel.

- *Clinically Driven Reintervention* is defined as procedures performed to address problems (complaints of leg pain/worsening pain, a progressing non-healing ulcer, new ulcer formation, or with or without the presence of an abnormal non-invasive test) that occur as a result of the index procedure are considered reinterventions. Purely diagnostic procedures are not included in this definition.

TECHNICAL SUCCESS

Successful completion of the endovascular procedure without major complications with attainment of ≤30% residual stenosis (visual estimate) of the treated lesion without the need for bailout procedures.

TRANSIENT ISCHEMIC ATTACK (TIA)

Focal neurologic abnormalities of sudden onset and brief duration (i.e., lasting less than 24 hours) that reflect dysfunction in the distribution of the affected artery. TIAs include transient monocular blindness (e.g., amaurosis fugax defined as a transient episode of monocular blindness, or partial blindness, lasting ten minutes or less) and transient hemispheric attacks.

VASOSPASM

The sudden, but transitory constriction of a blood vessel, potentially causing discomfort and limitation of distal blood flow.

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Attachment 1: Informed Consent Template

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Revision History

Rev.	Change	Date
1	Original issue of protocol for US IDE study.	30April2019
2	• Expanded data collection for all non-target lesion interventions (in both target and non-target limbs) performed post-index procedure • Clarified the use of alternative therapies within the target lesion for bailout purposes. • Clarified balloon inflation definitions for dissection and residual stenosis • Revised primary patency definition to include major amputation • Removed “device related” in statistical section • Added major amputation as a component of primary patency endpoint. • Removed target lesion occlusion from CEC adjudications. • Clarified determination of expectedness for SADEs and procedure-related SAEs • Definition of cardiac and non-cardiac death updated	28June2019
3	• Increased max enrollment per site from 35 to 40	19August2022

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