# Revolution™ Peripheral Atherectomy System for Lower Extremity Peripheral Arterial Revascularization

# (The REVEAL Study)

Device: Revolution™ Peripheral Atherectomy System

Protocol Number: REX-US-2017-001

Version: H; August 1, 2019

**IDE Number:** G160267

**Sponsor**
Rex Medical, L.P.
555 East North Lane, Suite 5035
Conshohocken, PA 19428

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Investigational Device Exemption for the Revolution™ Peripheral Atherectomy System

| **Investigator Name** | **Title** |
|---|---|
| **Site Name** | **Site Number** |

I have read the protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined therein.

I will provide copies of the protocol and all information on the device relating to past non-clinical and clinical experience, which were furnished to me by the Sponsor, to all physicians and other study personnel responsible to me who participate in this study, and will discuss this material with them to ensure that they are fully informed regarding the device and the conduct of the study.

I agree to keep records on all subject information (e.g., source documents and informed consent forms), device shipments and return forms, and all other information collected during the study, in accordance with local and national regulations.

| Investigator's Signature | Date |
|---|---|

## SYNOPSIS

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| Protocol Number: | REX-US-2017-001 |
| Investigational Device: | Revolution™ Peripheral Atherectomy System |
| Study Title | Revolution™ Peripheral Atherectomy System for Lower Extremity Peripheral Arterial Revascularization (REVEAL) |
| Sponsor | Rex Medical, L.P.<br>555 East North Lane, Suite 5035<br>Conshohocken, PA 19428 |
| Study Purpose | To evaluate the safety and effectiveness of the Revolution™ Peripheral Atherectomy System in the treatment of infrainguinal lower extremity peripheral arterial occlusive disease. |
| Study Population | Up to 121 subjects |
| Number of Sites | Up to 18 investigational sites in the United States |
| Study Design | A single-arm study of the Revolution™ Peripheral Atherectomy System in subjects with peripheral arterial disease (PAD). |
| Primary Endpoints | Primary Safety Endpoint:<br>The primary safety endpoint is freedom from 30-day Major Adverse Events (MAE), defined as the composite of all-cause mortality, clinically-driven target lesion revascularization (TLR), major target limb amputation, major target vessel perforation requiring surgical or endovascular repair and clinically-significant distal embolization in the target limb; as adjudicated by the independent Clinical Events Committee (CEC).<br>Primary Effectiveness Endpoint:<br>The primary effectiveness endpoint is technical success, defined by ≤50% diameter stenosis after atherectomy with the Revolution™ Peripheral Atherectomy System and prior to adjunctive therapy, as measured by the independent core laboratory on the post-atherectomy contrast angiogram. Effectiveness will be assessed for investigator-identified target lesions and will be calculated as a binary variable as the proportion of target lesions with technical success. |
| Secondary Endpoints | The following will be assessed as secondary endpoints of the study:<br>1. Change in % stenosis after treatment with Revolution™ Peripheral Atherectomy System, determined after atherectomy and prior to other adjunctive therapies, as measured by the angiographic core laboratory.<br>2. Procedural success as defined by target lesion residual stenosis of <30% at the conclusion of the index procedure, after |

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| | atherectomy and any adjunctive endovascular treatment, as measured by the angiographic core laboratory.<br>3. Assessment of the individual components of the primary safety endpoint (MAE); including all-cause mortality, major target limb amputation, clinically significant distal embolization, major target vessel perforation requiring surgical or endovascular repair, and clinically-driven TLR, measured through 30 days and at 6 months.<br>4. Minor unplanned target limb amputation rate through 30 days and 6 months;<br>5. Myocardial infarction through 30 days and 6 months;<br>6. Incidence of target vessel revascularization (TVR) through 30 days and 6 months;<br>7. Frequency of angiographic procedural distal embolization (symptomatic) in the target limb as confirmed angiographically by the core laboratory;<br>8. Primary patency of the target lesion at 30 days and 6 months, determined by duplex ultrasound or angiography;<br>9. Primary-assisted patency of the target lesion at 30 days and 6 months, determined by duplex ultrasound or angiography;<br>10. Secondary patency of the target lesion at 30 days and 6 months, determined by duplex ultrasound or angiography. |
| Patient Population | Subjects with symptomatic PAD eligible for treatment with the Revolution™ Peripheral Atherectomy System with atherosclerotic lesions of the superficial femoral, popliteal and tibial arteries will be eligible for inclusion in the study. |
| Inclusion Criteria | Subjects must meet the following criteria to be included in the study:<br>1. Age ≥ 18 years;<br>2. Willing and able to provide informed consent;<br>3. Ability to take at least one form of anti-platelet therapy.<br>4. Rutherford Categories 2, 3 or 4 in the target limb; Rutherford category 5 if no exposed bone, tendon or active infection;<br>5. Lesions to be treated with the study device must be located in the same limb;<br>6. Target lesion(s) located within the superficial femoral, popliteal or tibial arteries;<br>7. Target lesion(s) with stenosis ≥70% diameter reduction as measured by site-reported angiography;<br>8. Target lesion length(s) ≤150 mm; |

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| | 9. Target lesions(s) with reference vessel diameter (proximal and distal to target lesion) ≥2.0 mm and ≤4.0 mm. |
| Exclusion Criteria: | Subjects will be excluded from the study for:<br>1. Subjects in whom amputation above the ankle is necessary, irrespective of the success of revascularization;<br>2. In-stent restenosis within the target lesion;<br>3. Flow-limiting dissection, Type C or greater;<br>4. Target lesions within an autogenous or prosthetic bypass graft;<br>5. History of an endovascular procedure or open vascular reconstruction in the index limb within the last 30 days, including thrombolytic therapy;<br>6. Any open vascular surgical procedure planned in the target limb or endovascular procedures planned in the target vessel within 30 days after the index procedure;<br>7. Kidney disease of sufficient severity, in the Investigator's opinion, to contraindicate lower extremity angiography using standard or alternate contrast agents as per the local Standard of Care;<br>8. Pregnancy or breast feeding. A woman of child-bearing potential must have a negative pregnancy test within one week of index procedure;<br>9. Myocardial infarction or stroke within 2 months of enrollment;<br>10. Contraindication to antiplatelet, anticoagulant, or thrombolytic therapy;<br>11. Uncorrectable bleeding diathesis or platelet dysfunction or thrombocytopenia with platelet count < 125,000/μL, known coagulopathy, or INR > 1.5;<br>12. Known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pretreated in the opinion of the investigator;<br>13. History of heparin-induced thrombocytopenia;<br>14. Psychiatric disorder which, according to the investigator, has potential to interfere with provision of informed consent, completion of tests, therapy, or follow-up;<br>15. Clinical/angiographic evidence of distal embolization or acute thrombus;<br>16. Significant stenosis (>50% diameter reduction) or occlusion of inflow vessels that was not successfully treated (<50% residual stenosis without flow-limiting dissection) before the study intervention. |

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| Sample Size Calculation | Performance goals of 80% for safety and 76% for effectiveness have been established from prior studies. Enrollment of 121 subjects will provide 90% power, based upon a one-sided 97.5% exact binomial test, an anticipated 30-day MAE rate of 9%, acute technical success of 86%, and a 30-day attrition rate of approximately 10%. |
| Analytical Sets | The regulatory submission will be based on an approximate sample size of 121 subjects. Assuming a lesion-to-subject ratio of 1.5, approximately 165 target lesions will be evaluable for the primary effectiveness endpoint. Subset analyses will be performed for device effectiveness for superficial femoral/popliteal and tibial artery target lesions. |
| Pre-Enrollment Testing | Medical history, physical examination with vital signs and directed peripheral vascular examination, laboratory assessment, ankle-brachial or toe-brachial index, and patient-reported outcome measures. The diagnostic angiogram at time of the planned index procedure is performed prior to the point of enrollment in the study; eligibility is, in part, based upon the anatomic findings of the angiogram. |
| Follow-Up Schedule | Subjects will have required follow-up evaluations at the following time points:<br>1. Discharge;<br>2. 1 month post index procedure;<br>3. 6 months post index procedure; |
| Follow-Up Data Collection | 1. Adverse Events at the index procedure, hospital discharge, and through 6 months;<br>2. Rutherford Category at 1 and 6 months;<br>3. Ankle-brachial or toe-brachial index at 1 and 6 months;<br>4. Duplex ultrasound or angiography of the target vessel at 1 and 6 months. |
| Clinical Events Committee (CEC) | An independent CEC will review all primary safety endpoint events, unanticipated adverse device effects, and other important safety occurrences as specified in the CEC Charter. |
| Data Safety Monitoring Board (DSMB) | An independent Data Safety Monitoring Board (DSMB) will review safety data from the study at predetermined time points and as deemed necessary by the Sponsor or the DSMB Chair. The DSMB will make recommendations on protocol modifications and continuation of the study. |
| Principal Investigator | Dr. Jeff Carr, MD |

# 1. INTRODUCTION AND BACKGROUND

Infrainguinal peripheral arterial occlusive disease (PAD) is manifest over a spectrum of clinical presentations, ranging from the asymptomatic loss of peripheral pulses, leg claudication, to pain at rest, gangrene and limb-loss.[1] The magnitude of signs and symptoms is well correlated with the anatomic extent of disease.[2] Single-level, short arterial obstructions with moderate levels of stenosis may remain asymptomatic, while multilevel, long-segment occlusions often culminate in ischemic complications that threaten the viability of the limb.

With the advent of lower extremity angiography, definitive methods of lower extremity arterial revascularization gained popularity. Open surgical endarterectomy and bypass were employed which provided adequate channels for normalization of blood flow. When successful, symptoms of claudication and rest pain can be completely remediated and leg ulcerations will heal. Unfortunately, open surgical revascularization procedures represent significant challenges to patients with PAD, a population who often display other manifestations of systemic atherosclerosis including significant coronary artery and cerebrovascular disease. These comorbidities, amongst others, account for an undesirably high rate of morbidity and mortality following surgical revascularization, with perioperative morality rates approaching 5% in most series.[3-5]

On this backdrop, minimally-invasive techniques for lower extremity arterial revascularization gained a foothold. The advent of balloon angioplasty catheters (percutaneous transluminal angioplasty, or PTA) provided a percutaneous means to restore arterial flow, albeit with a trade-off between procedural morbidity and long-term durability.[6] Metallic stents entered the armamentarium of the peripheral interventionist a decade later, first as balloon-expandable stainless steel devices but later as more flexible and crush-resistant nitinol devices, most recently with antiproliferative drug-eluting coatings to discourage in-stent restenosis.[7-11] Drug-eluting balloons and bioresorbable polymer scaffolds were the most recent technological additions, each developed in an effort to limit the drawbacks of metallic stents as permanently implantable foreign bodies.[12-15]

Atherectomy was conceived early on as another method of revascularization available for patients with PAD.[16-19] Its value in the management of lower extremity peripheral arterial disease has been amplified in light of the difficulties associated with treating PAD with PTA alone; with or without drug-eluting devices. PTA is associated with many challenges including elastic recoil, dissection, and disruption of the internal elastic lamina.[20,21] Because of its debulking capability, atherectomy use has helped widen the spectrum of lesions associated with PAD that are amenable to revascularization.[21,22] Recurrent stenosis continues to be the primary issue limiting the long-term success of the revascularization methods used to treat PAD. While atherectomy may help to mitigate or overcome some of the limitations of PTA, it is difficult to designate one revascularization method most effective for PAD given the nature of the disease.

A study by Quevedo et al. compared primary patency rates at 12 months in patients with infrainguinal arterial disease who were treated with balloon angioplasty and/or stenting alone with those who received atherectomy in addition to angioplasty/stenting.[23] Two randomized studies were obtained and served as

the basis of the analysis. When directional atherectomy was used as stand-alone treatment, primary patency at 12 months approached 60%. The primary patency at 12 months approached 90% when orbital atherectomy was used in conjunction with angioplasty and stenting. Despite the apparent synergies between atherectomy and PTA, authors concluded that there was insufficient data to justify use of atherectomy as stand-alone treatment in management of patients with PAD.

# 2. INVESTIGATIONAL DEVICE

## 2.1. Overview

The Rex Medical Revolution™ Peripheral Atherectomy System is intended for use in peripheral vessels of suitable patients with atherosclerotic PAD.

## 2.2. Manufacturer

Rex Medical, L.P.
555 East North Lane, Suite 5035
Conshohocken, PA 19428

## 2.3. Model Numbers

The Revolution™ is available in the four different models, each with its own model number (**Table 1**).

**Table 1. Revolution™ models**

| Model Number | Name | Length (cm) | Bit Size (mm) | Minimal RVD (mm) | Maximal RVD (mm) |
|---|---|---|---|---|---|
| 2006145133 | Revolution™ | 145 | 1.33 | 2.00 | 2.49 |
| 2006145166 | Revolution™ | 145 | 1.66 | 2.50 | 2.99 |
| 2006145200 | Revolution™ | 145 | 2.00 | 3.00 | 4.00 |
| 2006060133 | Revolution™ | 60 | 1.33 | 2.00 | 2.49 |

RVD- Reference vessel diameter

## 2.4. Device Traceability

Lot number will be used to trace devices used in the study.

## 2.5. Intended Purpose of the Clinical Investigation

The purpose of this investigation is to evaluate the safety and effectiveness of the Revolution™ Peripheral Atherectomy System in the treatment of infrainguinal lower extremity peripheral arterial occlusive disease.

## 2.6. Indications for use

The Revolution™ Peripheral Atherectomy System is intended for use in atherectomy of the peripheral vasculature and to break apart and remove thrombus from the peripheral arteries inpatients with occlusive atherosclerotic disease.

## 2.7. Anticoagulation and antiplatelet therapy

The study device must not be used in subjects who cannot receive antiplatelet and in those who cannot receive systemic anticoagulant therapy.

The use of antiplatelet agents should be guided by the institutional standard of care. Subjects must receive aspirin at a dose of at least 80 mg per day, beginning at least one hour prior to the index procedure and continued through 6 months.[a]

The subject must be systemically anticoagulated during use of the Revolution™ device. Adequate anticoagulation with unfractionated heparin or another standard agent must be administered prior to introduction of the study device. The level of systemic anticoagulation should be monitored per institutional guidelines, using, for instance, the activated coagulation time or another suitable measure, and should be maintained at adequate levels until withdrawal of the study device from the circulation.

## 2.8. Device Description

The Rex Medical Revolution™ Peripheral Atherectomy System is a minimally invasive catheter-based atherectomy system used to treat patients who suffer from PAD. This system is designed to treat a broad range of plaque types both above and below the knee and may address many of the limitations associated with existing treatment options.

The Revolution™ Peripheral Atherectomy System consists of a sterile, single-use handle containing an electric motor and circuitry (**Figures 1-6**, below). The handle is equipped with an on/off button and speed select switch. The speed select switch allows the user to engage a treatment speed of 140,000 rpm or a guidewire rapid exchange speed of 12,000 rpm. The rapid exchange (REX) setting breaks static friction, thereby facilitating exchange over the guidewire. The ablating mechanism consists of a spheroid-shaped burr coated in 15 µm diamond grit at the distal end of a flexible drive shaft. There are three (3) burr diameters: 1.33 mm, 1.66 mm, and 2.00 mm. The burr is rotated at 140,000 rpm to facilitate plaque ablation. The ablated plaque is brought into the catheter where it is mechanically conveyed from the patient using an Archimedes Screw fixed on the outer surface of the drive shaft. The drive shaft is equipped with a central lumen which accommodates a Rex Medical supplied 0.014" guidewire. The catheter uses coaxial construction to accommodate independent infusion and aspiration functions. The proximal end of the handle is composed of an adapter with two ports: one for debris

[a] Discontinuation of antiplatelet therapy prior to 6 months for drug-related complications or for new or worsened medical conditions that increase antiplatelet agent-associated bleeding risk will not be considered to be a Protocol Deviation.

conveyance and the other for saline infusion. The system's power cable is designed to be plugged in to the supplied AC/DC converter which can be plugged into any standard 110V outlet.

The Revolution™ Peripheral Atherectomy System is designed for use with the silicone-coated Revolution™ Guidewire, also manufactured by Rex Medical. The Revolution™ Guidewire has a shaft diameter of 0.014″ and is made of stainless steel with a smooth finish. The spring tip configuration is atraumatic, radiopaque, and malleable to allow formation of a steerable system. Also supplied is a Guide Wire Torquer, a plastic device that attaches to the guide wire to provide a gripping surface for guide wire manipulation.

The following items (supplied by Rex Medical) are required for proper use of the Revolution™ Peripheral Atherectomy System:

1. Revolution™ Peripheral Atherectomy System Handle (**Figure 1**)
2. Revolution™ Peripheral Atherectomy System Power Supply (**Figure 2**)
3. Disposal bag (500 mL) for material conveyed out of the aspiration port (**Figure 3**)
4. Saline bag spike and infusion tubing (**Figure 4**)
5. Rex Medical Revolution™ Guidewire (**Figure 5**)
6. Guidewire Torquer and Clip (**Figure 6**)

The operating room should be equipped with the following items:

1. Guide catheter/sheath introducer
2. Standard IV pole
3. Sterile heparinized (10,000 IU/L) 0.9% normal saline
4. Fluoroscopic imaging equipment
5. Standard 110 V electrical wall outlet
6. Other equipment as needed for interventional procedures

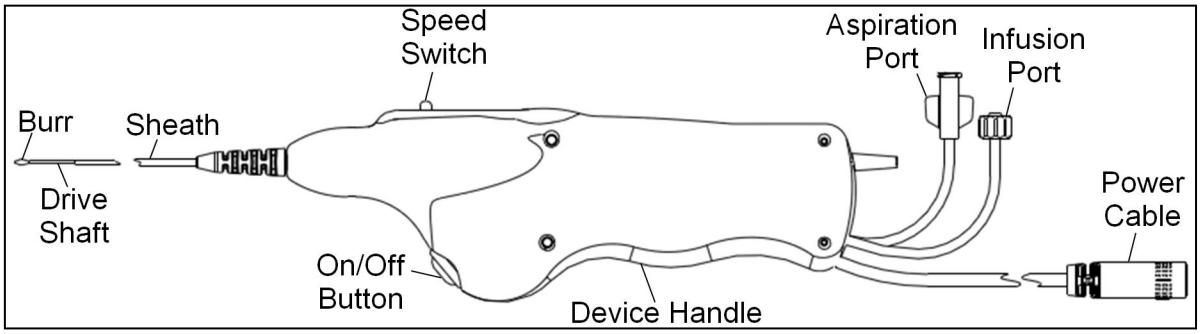


**Figure 1.** The Revolution™ Peripheral Atherectomy System Handle

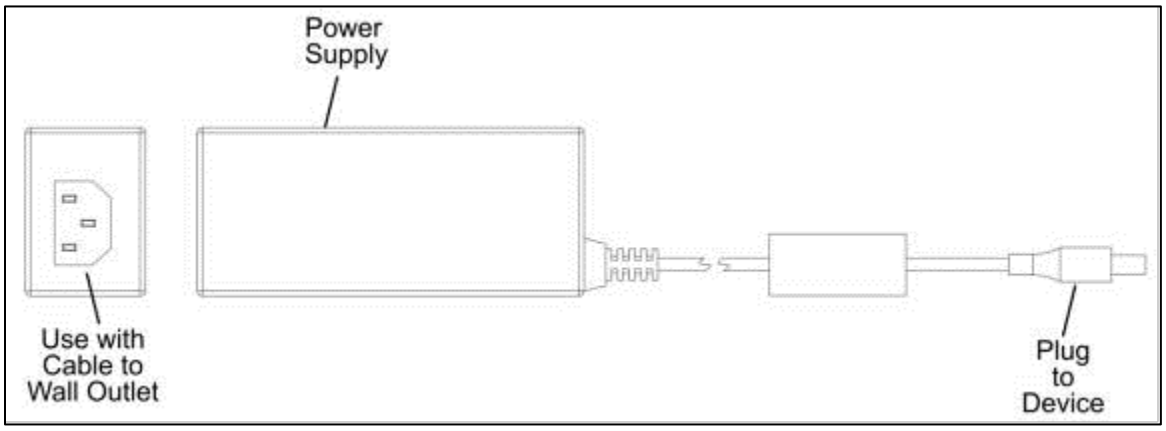


**Figure 2.** The Revolution™ Peripheral Atherectomy System Power Supply

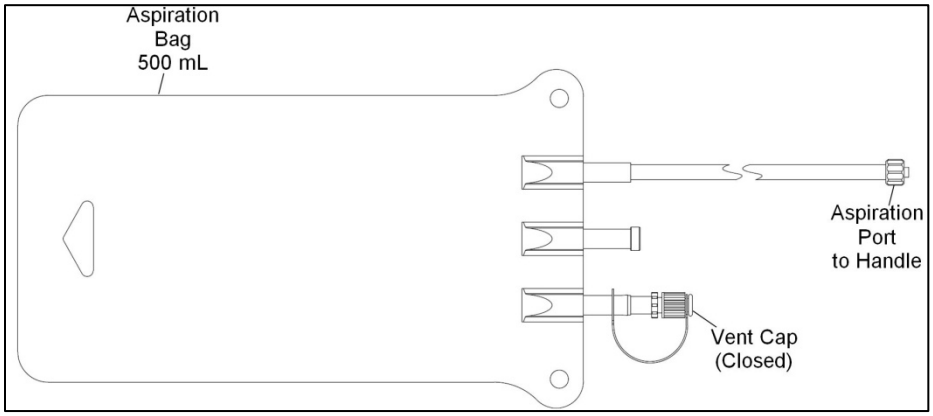


**Figure 3.** The Revolution™ Peripheral Atherectomy System Disposal

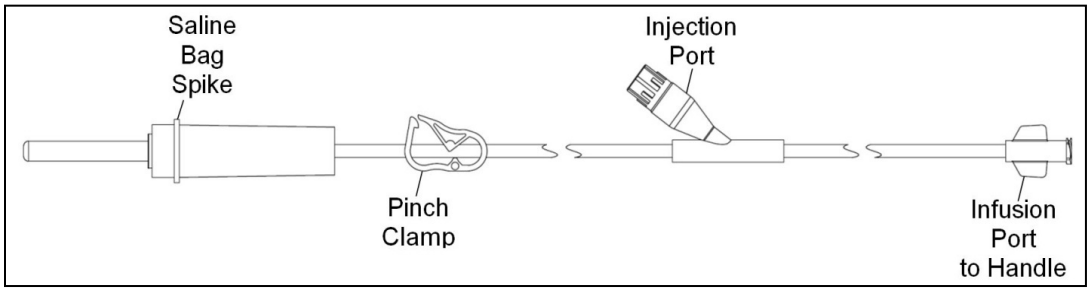


**Figure 4.** The Revolution™ Peripheral Atherectomy System Infusion Line

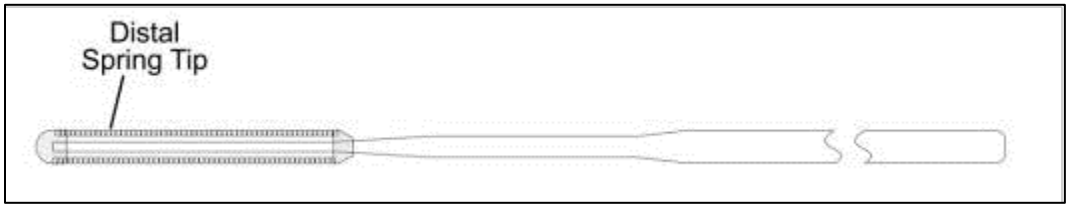


**Figure 5.** The Revolution™ Peripheral Atherectomy System Guidewire

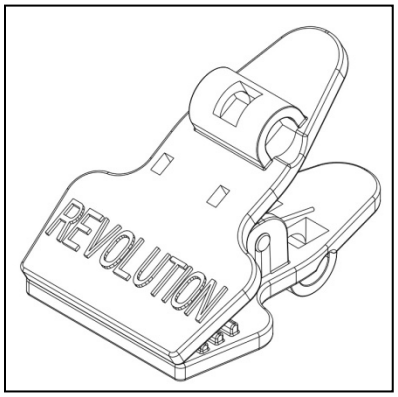


**Figure 6.** The Revolution™ Peripheral Atherectomy System Guidewire Torquer and Clip

## 3. PRIOR INVESTIGATIONS

The Sponsor, Rex Medical L.P. (Conshohocken, PA), has developed the study device known as the Revolution™ Peripheral Atherectomy System. The Revolution™ Peripheral Atherectomy System has yet to be formally evaluated in the US. This clinical investigation will allow the Sponsor to collect safety and effectiveness data regarding its Revolution™ Peripheral Atherectomy System.

## 4. STUDY OBJECTIVES

The objective of this study is to evaluate the safety and effectiveness of the Revolution™ Peripheral Atherectomy System in the treatment of infrainguinal lower extremity peripheral arterial occlusive disease.

Safety will be evaluated by assessing freedom from 30-day Major Adverse Events (MAE), defined as the composite of all-cause mortality, clinically-driven target lesion revascularization (TLR), major target limb amputation, major target vessel perforation requiring surgical or endovascular repair and clinically-significant distal embolization in the target limb; as adjudicated by the independent Clinical Events Committee (CEC).

Effectiveness will be evaluated by acute debulking, assessed by technical success (≤50% diameter stenosis) after atherectomy with the study device, prior to adjunctive therapy with balloon angioplasty, stent deployment or other interventions. Effectiveness will be evaluated from post-atherectomy contrast angiograms, as evaluated by the independent core laboratory. Effectiveness will be assessed for all investigator-identified target lesions and calculated as the proportion of investigator-identified target lesions with technical success.

Secondary objectives will consist of the following:

- Change in percent stenosis after treatment with Revolution™ Peripheral Atherectomy System, determined after atherectomy and prior to other adjunctive therapies, as measured by the angiographic core laboratory;
- Procedural success as defined by target lesion residual stenosis of <30% at the conclusion of the index procedure, after atherectomy and any adjunctive endovascular treatment, as measured by the angiographic core laboratory;
- Assessment of the individual components of the primary safety endpoint (MAE); including all-cause mortality, major target limb amputation, clinically significant distal embolization, major target vessel perforation requiring surgical or endovascular repair, and clinically-driven TLR, measured through 30 days and at 6 months.;
- Minor unplanned amputation rate through 30 days and 6 months;
- Myocardial infarction through 30 days and 6 months;
- Incidence of target vessel revascularization (TVR) through 30 days and 6 months;
- Frequency of angiographic procedural distal embolization (symptomatic) in the target limb as confirmed angiographically by the core laboratory;
- Primary patency of the target lesion at 30 days and 6 months, determined by duplex ultrasound or angiography;
- Primary-assisted patency of the target lesion at 30 days and 6 months, determined by duplex ultrasound or angiography.
- Secondary patency of the target lesion at 30 days and 6 months, determined by duplex ultrasound or angiography.

# 5. OUTCOME VARIABLES

## 5.1. Primary Safety Endpoint Definition

The primary safety endpoint is a composite endpoint triggered by the occurrence of any of five categories of events through 30 days after the index procedure.[b] These events are the following:

1. All-cause mortality- Death from any cause, from the point of enrollment through 30 days.
2. Clinically-driven TLR- Any revascularization of the target lesion that occurs after the subject has left the procedure room following the index procedure. TLR do not include adjunctive interventions performed during the index procedure, whether planned or for failed atherectomy or for complications of atherectomy. TLR are considered to be clinically-driven when they occur as a

[b] The index procedure is considered to occur on day 0; the first post-procedure day is day 1, and so on. The 30-day time point includes any events with a start date prior to 11:59PM on day 30.

result of restenosis >50% diameter reduction as measured angiographically or by duplex ultrasound (occlusion or stenosis with Peak Systolic Velocity Ratio >2.4).[c]

3. Perforation of the target vessel- Imaging evidence (standard contrast angiography, computed tomography angiography or open surgical/pathology visualization) of target vessel perforation from any cause. For angiography and CTA, perforation is defined by contrast extravasation outside of the adventitia.
4. Clinically-significant distal embolization- Target limb embolization documented on core laboratory-assessed angiography or with open surgery/pathology, accompanied by symptoms referable to the involved vascular bed.
5. Major amputation- Amputation of the target limb that results in limb shortening; i.e. is performed at or above the level of the malleoli.

### 5.2. Primary Effectiveness Endpoint Definition

The primary effectiveness endpoint is technical success defined as acute debulking resulting in a reduction of stenosis to ≤50% after treatment with Revolution™ Peripheral Atherectomy System from baseline and prior to other adjunctive therapies at the conclusion of the index procedure, as measured by the angiographic core laboratory.

Within any target lesion, stenosis is measured at the point of the minimum luminal diameter (MLD) over its shoulder-to-shoulder length.[d] The reference vessel diameter (RVD) is the interpolated diameter from the point just proximal to the point just distal to the target lesion. The percent stenosis is calculated as:

% Diameter Stenosis = 1 – MLD/RVD

## 6. STUDY DESIGN

The study population will include up to 121 subjects, male and female, who are appropriate candidates for endovascular treatment of infrainguinal lower extremity peripheral arterial occlusive disease with the Revolution™ Peripheral Atherectomy System.

### 6.1. Study Design

This single-arm study of the Revolution™ Peripheral Atherectomy System includes subjects with PAD and significant target lesions of the appropriate diameter, located within the superficial femoral artery (SFA), popliteal and tibial arteries.

[c] If an angiogram and a duplex ultrasound imaging study are discordant within any 30-day period, the angiographic results will supersede the duplex findings.
[d] The shoulder-to-shoulder length is determined visually using a Quantitative Vascular Angiography (QVA) software application. RVD is determined at the location of the MLD, linearly interpolated between the luminal diameters just proximal to and distal to each shoulder.

## 6.2. Informed Consent

Written, study-specific Informed Consent will be obtained from each subject prior to treatment with the Revolution™ Peripheral Atherectomy System. The Investigator will keep the original Informed Consent Form and a copy will be given to the subject. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Subjects will be consented for five years to allow for the ability to collect additional data, in the event that initial study results indicate a need for additional long-term information.

## 6.3. Inclusion Criteria

Subjects may be enrolled in the study if they meet the following criteria:

1. Age ≥ 18 years;
2. Willing and able to provide informed consent;
3. Ability to take at least one form of anti-platelet therapy;
4. Rutherford categories 2, 3, or 4 in the target limb; Rutherford category 5 if no exposed bone, tendon or active infection;
5. Lesions to be treated with the study device must be located in the same limb;
6. Target lesion(s) located within the superficial femoral, popliteal or tibial arteries;
7. Target lesion(s) with stenosis ≥70% diameter reduction as measured by site-reported angiography;
8. Target lesion length(s) ≤150 mm;
9. Target lesions(s) with reference vessel diameter (proximal and distal to target lesion) ≥2.0 mm and ≤4.0 mm.

A subject must have at least one target lesion that meets the anatomic inclusion criteria above. Other lesions that do not meet these criteria may be treated but must not be treated with the study device and will not be considered target lesions. Bilateral treatment with the study device is not permitted.

## 6.4. Exclusion Criteria

Subjects will be excluded from the study for:

1. Subjects in whom amputation above the ankle is necessary, irrespective of the success of revascularization;
2. In-stent restenosis within the target lesion;
3. Flow-limiting dissection, Type C or greater;
4. Target lesions within an autogenous or prosthetic bypass graft;
5. History of an endovascular procedure or open vascular reconstruction in the index limb within the last 30 days, including thrombolytic therapy;
6. Any open vascular surgical procedure planned in the target limb or endovascular procedures planned in the target vessel within 30 days after the index procedure;

7. Kidney disease of sufficient severity, in the Investigator's opinion, to contraindicate lower extremity angiography using standard or alternate contrast agents as per the local Standard of Care;
8. Pregnancy or breast feeding. A woman of child-bearing potential must have a negative pregnancy test within one week of index procedure;
9. Myocardial infarction or stroke within 2 months of enrollment;
10. Contraindication to antiplatelet, anticoagulant, or thrombolytic therapy;
11. Uncorrectable bleeding diathesis or platelet dysfunction or thrombocytopenia with platelet count <125,000/μL, known coagulopathy, or INR >1.5;
12. Known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pretreated in the opinion of the investigator;
13. History of heparin-induced thrombocytopenia;
14. Psychiatric disorder which, according to the investigator, has potential to interfere with provision of informed consent, completion of tests, therapy, or follow-up;
15. Clinical/angiographic evidence of distal embolization or acute thrombus;
16. Significant stenosis (>50% diameter reduction) or occlusion of inflow tract vessels that was not successfully treated (<50% residual stenosis without flow limiting dissection) before study intervention.

Treatment of iliac and common femoral artery lesions to gain access to a target lesion or to provide adequate inflow is permissible, but such inflow lesions must not be treated with the study device and will not be considered target lesions.

## 6.5. Study Populations

The point of enrollment in this study occurs when a study device first enters a subject's vasculature.[e] The following populations will be analyzed in the study:

**Intention to treat (ITT) analysis**: The ITT analysis will be performed on all enrolled subjects in whom the study device entered the vasculature, irrespective of adherence with the entry criteria, treatment actually received, subsequent withdrawal, or deviation from the investigational plan.[24]

**Per Protocol analysis**: The PP analysis will be performed on target lesions with core laboratory-determined RVD falling within the pre-specified anatomic eligibility criteria of ≤4.0 mm. The effectiveness endpoints will be determined using the PP analytic subset to exclude lesions where the largest bore (2.0 mm) study device is less than 50% of the RVD (see Section 7.3, page 22, below).[f]

[e] This point is defined as entry of the study device into the access sheath/guide at the level where the sheath/guide enters the subject's body.
[f] Use of the 2.0 mm bore in a vessel larger than 4.0 mm in diameter would not result in a lumen channel that exceeds 50% of the RVD. In other words, the residual stenosis after successful atherectomy would still not meet the criteria

# 7. STATISTICS AND DATA ANALYSIS

## 7.1. Statistical Methodology

The objective of the statistical design for this study is to evaluate the safety and effectiveness of the study device, as assessed in comparison to literature-derived performance goals.

The safety and effectiveness performance goals were determined from a literature review of atherectomy publications. A total of 19 studies were included in this review and, among these, 13 reported data referable to the primary safety endpoint and 7 reported data referable to the primary effectiveness endpoint. Studies with populations that overlapped the population of another study were excluded.

## 7.2. Primary Safety Endpoint

The primary safety endpoint for this study is a composite endpoint of any MAE within 30 days, as adjudicated by the CEC. MAE is defined as 30-day all-cause mortality, clinically-driven TLR, major target limb amputation, major target vessel perforation requiring surgical or endovascular repair and clinically-significant distal embolization in the target limb. The rate of MAE will be compared to a performance goal with the following null and alternative hypotheses:

$H_0$: $P_S \leq PG_S$ versus $H_A$: $P_S > PG_S$

where Ps is the proportion of subjects free from MAE through 30 days and $PG_S$ is the safety performance goal derived from the studies reporting the elements contained in the composite MAE endpoint.

The Exact binomial one-sided 97.5% confidence interval will be used to test the primary safety endpoint.

## 7.3. Primary Effectiveness Endpoint

The primary effectiveness endpoint is technical success, defined by ≤50% diameter stenosis after atherectomy with the Revolution™ Peripheral Atherectomy System, prior to adjunctive therapy, as measured by the independent core laboratory on the post-atherectomy contrast angiogram. Effectiveness will be assessed for all investigator-identified target lesions in the PP analytic group and will be calculated on a per-lesion basis.

$H_0$: $P_E \leq PG_E$ versus $H_A$: $P_E > PG_E$

for technical success; even though the device performed as designed. Since the eligibility criteria are site-determined, the subject may still be included in the ITT population but the lesion would be excluded from the PP analytic group.

where $P_E$ is the proportion of lesions with technical success, as defined by angiographically-determined ≤50% target lesion diameter reduction on the post-atherectomy core laboratory measurement.[g] The effectiveness performance goal, PGE, is technical success defined in the same manner, derived from the published literature.

The primary effectiveness endpoint will be calculated for those target lesions that fall at or below the specified acceptable reference vessel diameter of 4.0 mm, as determined by the core laboratory. Target vessels with diameters >4.0 mm will be excluded from the analysis, since even the largest bit size (2 mm) would not result in a post-atherectomy channel size of ≥50% RVD.

The primary effectiveness endpoint analysis will use the E+M approach for one sample correlated binary data with cluster size of one or two that accounts for correlations between multiple target lesions within the same subject.[h]

## 7.4. Study Success Criteria

The study will be considered a success if both the primary endpoints meet their respective Performance Goals. For the effectiveness endpoint, this translates into observing a one-sided 97.5% lower confidence limit (LCL) of the point estimate above 76% and for the safety endpoint it means observing a one-sided 97.5% LCL above 80%.

## 7.5. Secondary Endpoints

The following secondary endpoints will be studied:

1. Change in percent stenosis after treatment with Revolution™ Peripheral Atherectomy System, determined after atherectomy and prior to other adjunctive therapies, as measured by the angiographic core laboratory
2. Procedural success as defined by target lesion residual stenosis of <30% at the conclusion of the index procedure, after atherectomy and any adjunctive endovascular treatment, as measured by the angiographic core laboratory;
3. Assessment of the individual components of the primary safety endpoint (MAE); including all-cause mortality, major target limb amputation, clinically significant distal embolization, major target vessel perforation requiring surgical or endovascular repair, and clinically-driven TLR, measured through 30 days and at 6 months.;
4. Minor unplanned target limb amputation rate through 30 days and 6 months;
5. Myocardial infarction through 30 days and 6 months;
6. Incidence of TVR through 30 days and 6 months;

[g] Technical success is defined on the post-atherectomy angiogram, prior to adjunctive therapy with balloon angioplasty, stent deployment, or any other intervention.
[h] Shan, G. C. Ma. Efficient tests for one sample correlated binary data with applications. Stat Methods Appl, 23:175-188, 2014.

7. Frequency of angiographic procedural distal embolization (symptomatic) in the target limb as confirmed angiographically by the core laboratory;
8. Primary patency of the target lesion at 30 days and 6 months, determined by duplex ultrasound or angiography;
9. Primary-assisted patency of the target lesion at 30 days and 6 months, determined by duplex ultrasound or angiography.
10. Secondary patency of the target lesion at 30 days and 6 months, determined by duplex ultrasound or angiography.

## 7.6. Missing Data

Every effort will be made to minimize the amount of missing data. Recognizing the difficulty of avoiding some missing data, however, data imputation methods with sensitivity imputation analyses will be pre-specified in the Statistical Analysis Plan. Subjects with missing effectiveness data for target lesions (MLD at the conclusion of atherectomy) will be assumed to have missing data at random and will be imputed by random selection with replacement of data from target lesions with post-atherectomy measurements. The robustness of the multiple imputation outcome will be tested with a tipping point analysis encompassing all possible imputation outcomes.

## 7.7. Derivation of the Safety Performance Goal

The primary safety endpoint of 30-day MAE was available from the following 13 studies (**Table 2**):

**Table 2.** Safety Performance Goal Literature Summary

| Study | Subjects | Subjects with MAE | MAE Rate (%) |
|---|---|---|---|
| Sixt[25] | 89 | 14 | 15.7% |
| Zeller[26] | 172 | 22 | 12.8% |
| Sundaram[27] | 148 | 50 | 33.8% |
| AtheroMed Phoenix 510(k) report[28] | 105 | 4 | 3.8% |
| McKinsey[29] | 799 | 80 | 10.0% |
| Sixt[30] | 161 | 20 | 12.4% |
| Stoner[31] | 40 | 4 | 10.0% |
| Zeller[32] | 84 | 10 | 11.9% |
| Yancey[33] | 17 | 5 | 29.4% |
| CRAG[34] | 72 | 10 | 13.9% |
| Ramaiah[18] | 601 | 19 | 3.2% |
| Muck[35] | 125 | 14 | 11.2% |
| Safian[36] | 124 | 4 | 3.2% |

The weighted average MAE rate was 10.1%. Using a 10% margin and rounding up to the nearest percent, the performance goal for the primary safety endpoint, 30-day freedom from MAE, is 80%.

## 7.8. Derivation of the Effectiveness Performance Goal

The primary effectiveness endpoint of acute technical success from atherectomy prior to adjunctive therapy was assessed from a literature review (**Table 3**). The weighted average Technical Success rate was 86.0%. Using a 10% margin and rounding up to the next percent, the performance goal for the primary effectiveness endpoint of technical success is 76%.

**Table 3.** Effectiveness Performance Goal Literature Summary

| Study | Target Lesions | Target Lesions with Technical Success |
|---|---|---|
| Sixt[25] | 89 | 82 (92.1%) |
| AtheroMed Phoenix 510(k) report[28] | 123 | 117 (95.1%) |
| Sixt[30] | 164 | 124 (75.6%) |
| Zeller[32] | 131 | 126 (96.2%) |
| Von Polnitz[37] | 86 | 70 (81.4%) |
| Ramaiah[18] | 1258 | 1072 (85.2%)[i] |
| Avinger Pantheris 510(k) report[38] | 164 | 158 (96.3%) |

## 7.9. Sample Size

The PG of 80% has been established for the primary safety endpoint, based on a one-sided 97.5% exact binomial test. The 30-day MAE rate is anticipated to be approximately 9%. Under these assumptions, the required sample size to achieve a level of 90% power is 110 subjects (**Table 4**). Assuming 10% attrition over 30 days, initial enrollment of 121 subjects is necessary.

A PG of 76% has been established for the primary effectiveness endpoint. Anticipating an actual technical success rate of approximately 86%, and based upon a one-sided 97.5% exact binominal test, the required sample size to achieve a level of 90% power is 165 target lesions. Assuming a 1.5 ratio of subjects to treated target lesions, approximately 110 subjects will be necessary (**Table 5**). Since the primary effectiveness endpoint is determined at the time of the index procedure, no attrition has been taken into account.

[i] The TALON publication reported the results in 1258 target lesions, among which 132 required preliminary balloon dilatation to deliver the device and technical success (≤50% residual stenosis after atherectomy) was not achieved in 54 lesions. Technical success was calculated assuming there was no overlap between these cases; i.e. technical success was achieved in 1072 (1258 – 132 - 54) lesions.

**Table 4. Sample Size – Primary Safety Endpoint**

| **Primary Safety Endpoint** | |
|---|---|
| Performance goal | 80% |
| Anticipated freedom from MAE | 91% |
| Significance level | .025 |
| Statistical test | One-sided exact binomial test |
| Desired power level | 90% |
| Required sample size prior to 10% 30-day attrition rate | 110 |
| Required sample size after attrition adjustment | 121 |

**Table 5. Sample Size – Primary Effectiveness Endpoint**

| **Primary Effectiveness Endpoint** | |
|---|---|
| Performance Goal | 76% |
| Anticipated technical success rate | 86% |
| Significance level | .025 |
| Statistical test | One-sided exact binomial test |
| Desired power level | 90% |
| Required sample size (target lesions) | 165 |
| Estimated subjects required for required number target lesions* | 110 |

*Assumes 1.5 target lesions treated per subject; a ratio calculated from the studies in the atherectomy literature review

## 7.10. Demographics and Baseline Characteristics

The baseline demographics and anatomic characteristics of the treatment group will be presented with descriptive statistics.

## 7.11. Subgroup and Other Analyses

Subgroup analyses will be performed on target lesions of the superficial femoral, popliteal and tibial arteries. The analyses will comprise descriptive analyses of the primary and secondary effectiveness endpoints.

## 7.12. Changes to Planned Analyses

All analyses will be detailed in the Statistical Analysis Plan (SAP). Any changes to the planned analyses will be documented as amendments to the SAP and in the study report.

## 7.13. Interim Analyses

The Data Safety Monitoring Board (DSMB) will review safety data (including components of the primary effectiveness endpoint, since these may impact safety) to ensure that it is ethical to continue the study, based on the absence of unacceptable risks to the subject.

There will be a descriptive safety and effectiveness analysis of the primary endpoints after 25 subjects have reached the 30 day follow-up milestone. Enrollment will not stop during this analysis. The results of this analysis will not be made public before the formal primary endpoint analysis and may be used for regulatory submission(s).

## 7.14. Assessment of Data Poolability

Poolability of data across clinical study sites is justified on a clinical basis (i.e. all study sites use the same protocol) the sponsor monitors the site for protocol compliance, and the data gathering instruments are identical. The Food and Drug Administration also requires a statistical assessment of poolability. This is done by comparing the baseline characteristics across study sites. For categorical baseline variables, such as sex, a generalized Fisher's exact test or equivalent test will be used and for quantitative variables, parametric or non-parametric analysis of variance (general linear models or an equivalent procedure) will be used.

The above statistical analyses do not result in an impediment to pooling, but rather assess the balance of baseline covariates across study sites. If any baseline covariate is found to be statistically significant by this process, multivariate analyses will be done to determine if the imbalance affected study outcome. This is done by using both the variable found out of balance and study site as possible covariates.

It may be necessary to combine two or more low enrolling study sites into pseudo-sites to allow these analyses. Sites with fewer than 6 subjects will be ranked by enrollment from low to high. Starting from the lowest enrollment site, sites will be combined into a pseudo site until the combined size reaches the median enrollment among all sites. This process will be repeated until all resulting sites have enrollment equal to or greater than 6 subjects. This will be done in a manner to preserve the structure of the study and prevent bias.

Baseline characteristics to be considered as possible covariates are as following:

- Age
- Sex
- Coronary artery disease
- Chronic obstructive pulmonary disease
- Myocardial infarction
- Hyperlipidemia
- Cerebrovascular accident
- Hypertension
- Diabetes
- History of tobacco use
- History of peripheral vascular disease
- Rutherford Category
- ABI/TBI

If there are relatively few missing data points (e.g., <10%) for a given variable, a simple sex-specific imputation using the mean (for continuous variables) or median (for dichotomous or categorical variables) of the non-missing values will be done. If there are >10% missing, the variable will be excluded from the imputation analysis.

Poolability analysis will also be performed on the primary endpoints comparing across sites after adjusting for covariates difference. Logistic regression model will be utilized to include unbalanced covariates and site as an independent variable, and the study outcome as dependent variable to assess outcome difference. If the p-value of site effect is less than 0.10, further analyses will be undertaken to investigate the imbalance of the study outcome.

# 8. ASSESSMENTS AND FOLLOW-UP SCHEDULE

Subjects will undergo the assessments depicted in 6.

## 8.1. Screening/Baseline Assessment

An initial evaluation will be used to determine if a subject may be considered for enrollment. This evaluation includes an assessment of diagnostic testing that would have been done as part of a subject's routine care. The final disposition (e.g., enrollment, ineligibility, or decision by the subject or physician not to enroll) must be noted. The following must be completed in order to screen a potential subject for participation:

- Review inclusion/exclusion to ensure subject meets criteria.
- Provide a lesion morphology/characterization from lower extremity perspective.

If the subject meets all inclusion and exclusion criteria, and anatomical features for the atherectomy procedure, the subject may be invited to participate in the study. Clinical center personnel will complete a Device Order Form and fax or email it to Rex Medical.

The data captured for the Screening Visit may be gathered over the course of more than one office visit; however, the data must have been obtained within 30 days of the scheduled procedure date. Specifically, the following windows apply to these assessments:

- Duplex Ultrasound or angiography – Within 90 days of index procedure
- Ankle-Brachial Index/Toe-Brachial Index – Within 30 days of index procedure
- Rutherford Classification – Within 30 days of index procedure
- Baseline Labs – Within 30 days of index procedure

The following procedures will be performed at the Screening visit prior to the procedure. All data must be recorded in the subject's case report form (CRF):

- Demographic information
- Physical examination
- Medical history including risk factors
- Patient-reported outcomes questionnaire
- Serum or urine pregnancy test for females of childbearing potential who must have a negative test at baseline and must be using a medically acceptable method of birth control or be postmenopausal or surgically sterile. Acceptable methods of birth control include: barrier method with spermicide, steroidal contraceptive, contraceptives in conjunction with a barrier method, intrauterine device (IUD), or abstinence.

Clinical laboratory tests are expected to be performed at this visit to establish baseline levels (i.e., creatinine, platelet counts and INR if subject is on warfarin). The panel of tests standardly performed at the institution for patients with similar conditions related to PAD should be considered. It is recognized that specific panels may vary between institutions. Laboratory data will not be specially analyzed but will be used only to support adverse event evaluations.

## 8.2. Point of Enrollment

Subjects will be consented prior to the index procedure, at a point where the anatomic eligibility criteria may be unknown to the Investigator. Enrollment in the study will occur at the point of insertion of the study device into the vasculature, when the device enters the portion of the sheath/guide that resides within the subject's arterial tree.

## 8.3. Treatment Assessment

Atherectomy using the Revolution™ Peripheral Atherectomy System is considered the treatment phase of the study. The procedure is conducted under fluoroscopic/angiographic guidance. Refer to the Instructions for Use (IFU) for techniques and methods for device deployment.

Anticoagulation therapy to ensure an activated clotting time of 250 – 300 seconds is recommended. Investigator discretion is advised regarding antiplatelet therapy and blood pressure adjustment.

Subjects who require conversion to open surgery due to treatment failure with the device will be followed at each of the follow-up visits specified in **Table 6**.

The following data are to be recorded on the subject's Treatment CRF.

- Procedure time (first cut to last stitch)
- Device runtime, passes and issues
- Description of adjunctive therapy used post-atherectomy
- Blood loss and replacement fluids (blood products) administered
- Vascular access artery
- Proximal device placement location
- Required additional procedures prior, post and/or during atherectomy procedure
- Anticoagulation use during the procedure (agent, total dose)
- AE observation, evaluation, and treatment

**Table 6. Schedule of relevant assessments**

| Assessment | Screening/ Baseline | Treatment | Discharge | 1m ± 1 week | 6m ± 2 weeks | Unscheduled Visits[j] |
|---|---|---|---|---|---|---|
| Informed consent | Within 30 days of index procedure | | | | | |
| Medical history | Within 30 days of index procedure | | | | | |
| Verify inclusion/exclusion criteria | Within 30 days of index procedure | | | | | |
| Pregnancy testing for female patients of childbearing potential | Within 7 days of index procedure | | | | | |
| Physical examination with peripheral vascular assessment | Within 30 days of index procedure | | | | | X |
| Examination of access site and assessment of healing | | | X | | | |
| Ankle- or toe-brachial index | Within 30 days of index procedure | | | X | X | X |
| Rutherford Category | Within 30 days of index procedure | | | X | X | |
| Duplex ultrasound examination or angiography | Within 90 days of index procedure | | | X | X | X |
| Adverse event assessment | | X | X | X | X | X |
| Patient-reported outcome questionnaires | Within 30 days of index procedure | | | X | X | |

## 8.4. Hospital Discharge Assessment

Subjects will be evaluated during the time after procedure completion and prior to hospital release. The following information will be collected on the Hospital Discharge CRF:

- Time spent in ICU (hours) and hospital (days)
- Examination of incision site and assessment of healing
- AE observation
- Replacement fluids (blood products) administered post procedure

[j] Ankle- or toe-brachial indices and duplex ultrasound/angiography are only required at unscheduled visits if the reason for the unscheduled visit was related to target limb symptoms.

## 8.5. Follow-Up Assessment

Follow-up evaluation will be scheduled for 30 days (±1 week) and 6 months (±2 weeks) post-procedure. The following assessments and procedures will be performed at the 30-day and 6-month follow-up visits:

- Lesion morphology/characterization assessed by duplex ultrasound/angiography
- AE observation

## 8.6. Secondary Interventions

Subsequent to treatment, conditions warranting additional treatment (e.g., restenosis) may present. Any intervention taken to treat a condition involving the initially-treated lesion shall be documented on the Additional Treatment CRF. Additional Revolution™ devices may be provided for conditions involving the initially-treated lesion. Since such procedures would be secondary interventions, repeating the determination of eligibility and consenting are not required unless mandated by institutional policies.

Additional Revolution™ devices may not be used for other lesions or conditions without prior written approval from the Sponsor. Such procedures must be presented in advance to the US Food and Drug Administration (FDA) and Institutional Review Board (IRB) unless deemed emergent. In either case, the use of the Revolution™ device for other lesions/conditions shall be treated as a protocol deviation.

## 8.7. Unscheduled Post Treatment Follow-up Visits

If a subject returns to the institution between scheduled follow-up visits for matters related to the study procedure, the visit will be treated as an unscheduled visit and the assessments completed at this visit will be done at the discretion of the Investigator. CRF pages are provided for unscheduled visits and contain the same information as all the follow-up visits, in addition to the reason for the visit.

## 8.8. Withdrawals and Loss to Follow-up

Participation is completely voluntary and each subject is free to withdraw from the study at any time. An investigator also has the right to withdraw the subject from the study in the event of reasons concerning the health or well-being of the subject, or in the case of lack of cooperation. Should a subject decide to withdraw for any reason, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal must be made and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal must be recorded on the subject's End of Study CRF. If the reason for the withdrawal is a device-related or procedure related AE, the event must be reported to the Sponsor and recorded in the CRF.

If the procedure is aborted, the subject does not need to complete the follow-up assessments, unless the subject is converted to surgical repair. The subject's enrollment roster position may not be made available to other subjects.

If a subject dies during the course of the study, the Sponsor will request an autopsy provided the subject authorized an autopsy in the event of death during the course of the study. Autopsy observations should include documentation of condition of body organs and determination of device and/or procedure relationship to death.

All efforts will be made to retain subjects in order to collect data at all the follow-up visits (30 days, 6 months). Due diligence in reaching the subject must be made by:

- Two documented telephone contact attempts, emails, or regular postal mail letters; and
- Certified letter

After the above attempts were made, if no response is obtained, the final evaluation of a given subject will be the last visit at which study-related procedures were performed on that subject. The End of Study CRF page will need to be completed and communication attempts will need to be documented.

# 9. STUDY MANAGEMENT CONSIDERATIONS

## 9.1. Data Management: Collection of Clinical Data

The Sponsor and/or assigned designee will be responsible for the processing and quality control of the data. Source data for safety will be retained for at least 2 years after the termination/completion of the study or after the approval/withdrawal of the marketing application, whichever occurs later. All other source data, source documents, CRFs, copies of protocols and protocol amendments, device accountability forms, correspondence, subject identification lists, informed consent forms, and other essential documents must also be retained for a period of at least 2 years as detailed above. Rex Medical, L.P. will inform the investigator/institution when these documents are no longer required to be retained.

No study document or image will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to the Sponsor.

## 9.2. Protocol Modifications

No changes from the final approved (signed) protocol will be initiated without the IRB's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration. The Principal Investigator will acknowledge the amendment by signing the Protocol Agreement.

### 9.3. Protocol Deviations

A protocol deviation is the non-adherence to or divergence from the protocol-specific study procedures. For example, violations of the inclusion and exclusion criteria, deviations from the schedule of required follow-up assessments, improper or lack of consent, and lack of IRB approval, would all be considered protocol deviations. A protocol deviation undertaken to protect the life or physical well-being of the patient in an emergency is a special circumstance that must be reported to the Sponsor and the reviewing IRB within 5 working days. The Sponsor must report the deviation to the FDA within 5 working days after the Sponsor learns of the deviation. No other type of prospective protocol deviation is permitted without prior approval. A record of all protocol deviations will be maintained and reviewed throughout the conduct of the study. The Sponsor will address deviations and take appropriate corresponding action. Continued non-compliance with the study protocol may lead to termination of the Investigator's participation in the study.

Subject eligibility for the study is determined by site-measured anatomic criteria; not by core laboratory values. For this reason, enrollment of subjects with core laboratory-determined anatomic measurements on the baseline, pre-interventional angiogram will not be protocol deviations.

### 9.4. Information to Study Personnel

The Investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting the study procedures and during the course of the study (e.g., when new staff become involved). The Investigator must ensure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities.

The monitor is responsible for explaining the protocol to all study staff, including the Investigator, and for ensuring their compliance with the protocol throughout the study. Additional information will be made available during the study when new staff become involved in the study, and as otherwise agreed upon with either the Investigator or the monitor.

## 10. ASSESSMENTS OF SAFETY

### 10.1. Defining Adverse Events

An adverse event is an untoward medical occurrence or exacerbation of an existing medical condition subsequent to the experimental therapy. Adverse events are rated in several ways:

- Severity (mild, moderate, severe)
  - ***Mild*****:** No limitation of usual activities, no therapy or only symptomatic therapy required to treat the injury or illness.
  - ***Moderate*****:** Some limitation of usual activities or specific therapy is required.
  - ***Severe*****:** Inability to carry out usual activities, hospitalization, emergency treatment, life threatening events, or death.

- Anticipated (anticipated, not anticipated)
- Device and procedure relationships (unrelated, possibly related, definitely related, or relationship unknown)

  - ***Unrelated:*** The clinical event is completely independent of study procedure/study device and/or evidence exists that the event is definitely related to another etiology.

  - ***Possibly related:*** The clinical event occurs within a reasonable time sequence to study procedure/study device and there is some evidence to "possibly" suggest a causal relationship. However, the influence of other factors such as underlying disease, concomitant medications, or concurrent treatment may have contributed to the event.

  - ***Definitely related:*** The clinical event occurs in a plausible time relationship to study procedure/study device and cannot be explained by any concurrent disease or other devices, drugs or chemicals.

  - ***Relationship unknown*****:** The relationship to the study procedure/study device is not known.

Adverse events will be categorized as either serious or non-serious. A Serious Adverse Event (SAE) is an event that meets at least one of the following:

- Is fatal
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Results in permanent impairment of a body function or permanent damage to a body structure
- Results in hospitalization or prolongs a hospitalization
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

An MAE is a subcategory of adverse events that include any of the primary safety endpoints occurring within 30 days of the index procedure. An adverse device effect (ADE) is any unwanted and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device and any event that is a result of user error. A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of the consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune. An unanticipated adverse device effect (UADE) is defined as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary

application), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects."

Section 15.1 (page 44, below) includes a list of possible adverse events associated with endovascular repair, including those events considered major device-related events and major morbidity. These events are considered reportable at all time points throughout the trial and require submission to the Sponsor.

Events not captured in these two categories are not considered in the primary effectiveness or primary safety analyses, regardless if they are device-related or serious. These events must nonetheless be documented on the Adverse Event CRFs. Additionally, any event with an outcome of death must be reported.

### 10.2. Reporting of Adverse Events

In addition to events considered in the primary effectiveness and primary safety analyses, all device- and/or procedure-related adverse events, as well as events resulting in death, must be captured on the Adverse Event Case Report Form. The report should include, wherever possible, severity, duration, outcome, and the Investigator's written medical judgment as to the relationship of the adverse event to the study device, procedure, or underlying disease (i.e., not related, possibly related, definitely related, or relationship unknown).

All SAEs must be reported to the Sponsor or its Contract Research Organization (CRO) within 5 business days of the Investigator's knowledge of the event. The event is reported in the electronic data capture system. IRB notification of the adverse event may also be required, depending on the conditions of approval or requirements of the respective committee. Any unanticipated adverse device effects must be reported to the Sponsor/CRO within 1 working day from when the Investigator first learns of it.

Non-serious reportable adverse events are to be submitted via the electronic data capture system in a timely fashion. Certain reportable events may require adjudication; therefore, supporting documentation must be sent to the Sponsor/CRO.

## 11. DEVICE ACCOUNTABILITY

### 11.1. Accountability and Procedures

a.) Each device shipment must be documented on the Device Accountability Log and include the receipt, dispensing, and return of investigational devices.
b.) When a shipment is received, the Investigator (or designee) must record on the Device Accountability Log the date received and the Catalog and Lot Number of each device. It is recommended that the Packing List also be signed and dated.
c.) Investigational devices must be kept in a secure, limited access storage area under recommended storage conditions (room temperature).

d.) During the course of the study, the following information must also be noted on the Device Accountability Log:
- Identification number of the subject for whom the device was intended
- Procedure date

e.) The Device Accountability Log must be readily available for inspection by representatives from the Sponsor, the IRB, and/or other relevant regulatory authorities at any time.

f.) The Device Accountability Log and device storage locations will be reviewed during monitoring visits.

g.) All unused investigational devices must be returned to Rex Medical L.P. once it is determined they will not be used. Upon completion of the study, all unused investigational devices must be returned to Rex Medical L.P., if any remain at the site. The monitor is to verify return.

# 12. STUDY ADMINISTRATION

## 12.1. Site Initiation

A Site Initiation Visit (SIV) will be conducted by the Sponsor or other appropriate designee, for example, its CRO, to ensure that all study supplies are present, to ensure proper training of the Investigator and study staff members in study-specific procedures, to ensure regulatory requirements are fulfilled prior to enrollment of the first study subject at a site, and to verify the site facilities and equipment are appropriate for conduct of the study.

The following items will be reviewed at the Site Initiation Visit. All training will be documented and must contain signatures of participants:

a) Introduction and overview of agenda
b) Obligations of the Investigator, including his/her responsibilities to ensure only appropriately qualified staff participate in the study conduct, and notification to the Sponsor or its CRO of any change in staff listed on the Delegation of Authority (refer to the site's Regulatory Binder) during the course of the study
c) Protocol (overall review including, but not limited to, inclusion/exclusion criteria, recruitment/withdrawal of subjects, study restrictions);
d) Completion and maintenance of the Delegation of Authority
e) Adverse experience reporting and unanticipated adverse device effect (UADE) reporting
f) Case Report Forms (procedures, corrections, timely completion, retention)
g) Source document preparation and retention
h) Role of the IRB
i) Informed Consent Process
j) Study file documents and document retention (ensure all pertinent regulatory documents are collected prior to the site starting the study)
k) Clinical supplies and device management (storage and accountability; device dispensing, labeling, and packaging)

l) Clinical laboratory facilities
m) Requirements for reporting any clinical data back to the Sponsor. (e.g., annual and final reports)
n) Monitoring schedule/plan
o) Other items that should be discussed: background and purpose of the study, previous studies/data, regulatory requirements, policy for publishing trial results, special equipment (if necessary).

## 12.2. Study Monitoring

Interim monitoring visits will be conducted by Rex Medical L.P. personnel or other appropriate designees (e.g., a Contract Research Organization) to ensure compliance with standard operating procedures (SOPs), the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary liaison between the Sponsor and the Investigator. The main responsibilities of the monitor are to visit the Investigator before, during, and after the study to ensure adherence to the protocol; to verify all data are correctly and completely recorded and reported; and confirm that informed consent is obtained and recorded for each subject before study participation.

The study monitor will contact and visit the Investigator at regular intervals throughout the study. The monitor will be allowed to check and verify the various records (CRFs and other pertinent source data records) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of the study progress, other Sponsor personnel may accompany the study monitor on visits to the study center. The Investigator and assisting staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits.

## 12.3. Study Termination

Rex Medical L.P. and applicable regulatory authorities have the right to terminate the entire study or a particular study site at any time. Situations that could warrant study termination include, but are not limited to:

a) Increased incidence of adverse experiences and/or the severity of such, suggestive of a potential, device-related health hazard
b) Insufficient subject enrollment
c) Recurrent protocol non-compliance, violations or deviations
d) Inaccurate, incomplete, and/or untimely data recording (>2 business days) on a recurrent basis
e) Lack of cooperation with monitoring visits (e.g., failure to adequately prepare for visits, address action items from one visit to the next, or provide access to medical records)

## 12.4. Data Handling and Recordkeeping

### 12.4.1. Completing, Signing and Archiving Case Report Forms

The Investigator must keep a separate subject identification list showing enrollment numbers, names, and dates of birth to allow unambiguous identification of each subject included in the study. It is recommended a note be made in the medical record that the subject is participating in a clinical research study.

The required data will be recorded on the Case Report Forms (CRFs). Clinical study data will be collected using electronic case report forms (eCRFs). A web-based electronic data capture (EDC) database will be used to record and manage study data. eCRF completion guidelines, the instructions for electronic data-entry, will be developed in conjunction with the sponsor, the CRO, and/or the EDC vendor. The CRFs will be completed electronically or legibly in black or blue ink, with reasons documented for missing data. All eCRFs must be kept in good order and updated so they always reflect the latest observations on the subjects participating in the study.

The Investigator will sign the appropriate pages of the CRF and source documentation. eCRF corrections will be made electronically and signed electronically by the Investigator. An embedded audit trail will capture the date, time and user making updates and changes to the electronic data.

Because it is important to have proper data collection in a timely manner, within 2 business days, the Investigator/Study Coordinator shall complete the eCRFs and provide them to the monitor upon request. When the monitor requests additional data or clarification of data for the eCRF, the request must be answered satisfactorily before the next monitoring visit.

### 12.4.2. Data Management and Archiving

The Sponsor will be responsible for the processing and quality control of the data. Source data for safety will be retained for at least 2 years after the termination/completion of the study or after the approval/withdrawal of the marketing application, whichever occurs later. All other source data, eCRFs, copies of protocols and protocol amendments, device accountability forms, correspondence, subject identification lists, informed consent forms, and other essential documents must be retained for a period of at least 2 years after the last approval of the marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational device. Rex Medical will inform the Investigator/ institution when these documents are no longer required to be retained.

No study document or image will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to the Sponsor.

#### 12.4.3. Direct Access to Source Data/Documentation

The Sponsor, auditors, and health authority inspectors (or their agents) will be given direct access to source data and documentation (e.g., medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

The Investigator must maintain, at all times, the primary records, (i.e., source documents) of each subject's data. Examples of source documents are hospital records, office visit records, examining physician's findings or progress notes, consultant's written opinion or notes, laboratory reports, device inventory, device label records, and CRFs that are used as the source.

The Investigator will maintain a confidential subject identification list that allows the unambiguous identification of each subject. All study-related documents must be kept until notification by Rex Medical L.P.

## 13. ETHICS

### 13.1. Informed Consent

Written informed consent must be obtained for each subject before any study-specific procedures or assessments are done and, specifically, prior to the subject being treated with the Revolution™ Peripheral Atherectomy System. Written informed consent will be obtained after the aims, methods, anticipated benefits, and potential hazards are explained.

If required by institutional policy, informed consent will be obtained prior to review of Baseline and Screening data. A Screening Consent Form may also be available to secure permission from the subject for reviewing prospective subject information (if requested/required by site or IRB policy) prior to the subject agreeing to participate in the trial and signing the study-specific Informed Consent Form.

The subject's willingness to participate in the study will be documented in writing in a study-specific Informed Consent Form, which will be signed and dated by the subject or Legally Authorized Representative. The Investigator will keep the original consent form and a copy will be given to the subject. It will be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Subjects will be consented for five years to allow for the ability to collect additional data, in the event that initial study results indicate a need for additional long-term information (i.e., during the post-approval phase).

### 13.2. Institutional Review Board (IRB)

This study must be approved by an appropriate IRB at each investigational site. Securing the approval is the responsibility of the Investigator, as defined by ISO 14155-1 and FDA regulations (21 CFR Part 56) prior to starting the study.

The Sponsor must receive a copy of the IRB approval letter (or equivalent documentation) for the study protocol and Informed Consent Form before the study can be started at that site or devices shipped to that Investigator.

The IRB and Sponsor must approve any significant changes to the protocol as well as a change of Principal Investigator. Documentation of the IRB approval must be provided to the Sponsor. Records of all study review and approval documents must be maintained by the Investigator in the Regulatory Binder and are subject to inspection by the Sponsor or regulatory authority during or after completion of the study. Serious Adverse Events and deaths must also be reported to the IRB and Sponsor (reference Section 10 for reporting instructions).

The Investigator must notify the IRB, as per their reporting guidelines, and the Sponsor when he or she deviates from the protocol. The Sponsor must be notified of all relevant action taken by the IRB and must receive a copy of all study-related correspondence between the Investigator and the IRB.

The IRB must receive notification of the completion of the study and final report within 3 months of study completion or termination. A copy of these reports must be provided to the Sponsor. The Investigator must maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted.

## 13.3. Confidentiality Regarding Study Subjects

The Investigator must ensure that the privacy of all subjects, including their personal identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the Sponsor, subjects will not be identified by their names, but by an individual identification code (i.e., initials and identification number).

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRFs. The monitor may conduct source-document verification on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

## 13.4. Clinical Events Committee

The CEC (made up of independent physicians who are not participants in the study. The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study which are based on the protocol. At the onset of the study, the CEC will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. All members of the CEC will be blinded to the primary results of the trial. The CEC will review and adjudicate appropriate clinical events on a regular basis. The events requiring adjudication will include those related to the device and to the primary safety and effectiveness endpoints, guided by a CEC charter.

## 13.5. Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will be responsible to assure the study is being conducted ethically and to adjudicate all possibly and definitely device- and/or procedure-related serious adverse events. The DSMB membership is represented from the key medical disciplines involved with endovascular repair, and may include an external biostatistician. None of the members is directly involved with the clinical trial and all possess endovascular experience. The Sponsor has contracted a Clinical Research Organization to organize, facilitate, and document meetings for the DSMB for this trial. The DSMB will meet regularly and as necessary, guided by a DSMB charter.

## 13.6. Core Reference Laboratory

A central core reference laboratory will independently evaluate duplex ultrasound and angiographic imaging data collected at participating institutions. All protocol-specified imaging studies must be sent to the Core Laboratory for evaluation. Refer to the Core Lab Manual for details about the identified laboratory and instructions for submitting data.

## 13.7. Participating Institutions and Investigators

Study sites and Investigators will be selected based on a variety of factors including, but not limited to, experience with endovascular techniques, access to required facilities and equipment, sufficient and adequately trained personnel, and availability of potential subjects. The criteria used for determination will be documented. No other centers/institutions are intended to participate in this study without permission from the relevant regulatory authority.

## 13.8. Agreements

All Principal Investigators and their Sub-Investigators or Co-Investigators must sign an Investigator Agreement. Rex Medical L.P. (or the authorized CRO) must receive a copy of the signed Investigator Agreements before the study may be started at that institution or devices shipped. Any Investigators joining the study after the site has been initiated may not receive devices or participate until an agreement is signed and received by the Sponsor.

## 13.9. Responsibilities

Investigator responsibilities include, but are not limited to, the following:

a.) Conducting the study in accordance with this investigational plan, signed agreement, and applicable regulations protecting the rights and safety of study subjects
b.) Informing all subjects that the device being utilized is for investigational purposes only, and ensuring that the requirements relating to obtaining informed consent and IRB approval are met
c.) Ensuring that informed consent is obtained for each study subject in accordance with applicable regulations (e.g., ISO 14155-1, 21 CFR Part 50)

d.) Ensuring that IRB approval is secured prior to starting the study and ensuring continuing review and approval as required throughout the investigation
e.) Ensuring all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations, are adequately qualified and trained, and meet their commitments
f.) Maintaining adequate and accurate records and ensuring those records are available for inspection at any time
g.) Ensuring that conducting the study does not give rise to conflict of interest (financial disclosure is required)
h.) Controlling of all investigational devices under investigation.

# 14. DATA SECURITY AND SCIENTIFIC INTEGRITY

## 14.1. Access to Data

The Sponsor, auditors, and health authority inspectors (or their agents) will be given access to source data and documentation (e.g., medical charts/records, laboratory test results, printouts, videotapes, etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

The Investigator must maintain, at all times, the primary records (source documentations) of each subject's data. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, device inventory, device label records, and CRFs that are used as the source.

The Investigator will maintain a confidential subject identification list that allows the unambiguous identification of each subject. All study-related documents must be kept until notification by Rex Medical L.P.

## 14.2. Security and Confidentiality

The Investigator must ensure that the privacy of all subjects, including their personal identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the Sponsor, subjects will not be identified by their names, but by an identification code (i.e., subject number).

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRFs. The monitor may perform source data verification on behalf of the Sponsor or regulatory authorities. Personal medical information will always be treated as confidential.

# 15. RISK ANALYSIS

## 15.1. Risks to the Subjects

Treatment with the Revolution™ Peripheral Atherectomy System is a procedure that poses significant risks to the subject, although these risks are not expected to be greater than with the current standard of care; endovascular treatment or open surgery. A summary of some of the known risks are identified in Table **7**, below; however, there may be risks that are not known or are unforeseen at this time. The risks include those related to the device and to the procedure, including those related to concomitant medications used periprocedurally and during follow-up.

Table 7. **Known risks of atherectomy**

| **Event Category** | **Event** |
|---|---|
| Cardiac | Myocardial infarction |
| | Congestive heart failure |
| | Arrhythmia |
| | Valve disorders; stenosis and insufficiency |
| | Hypertension |
| | Hypotension |
| Wound | Wound infection |
| | Wound pain |
| | Wound dehiscence |
| | Serous wound drainage |
| | Lymphorrhea |
| | Hematoma |
| | Ecchymosis |
| Peripheral vascular | Vessel perforation |
| | False aneurysm formation |
| | Arterial dissection |
| | Mural thrombus formation |
| | Vessel occlusion |
| | Arteriovenous fistula |
| | Distal embolization |
| Venous | Deep venous thrombosis |
| | Pulmonary embolism |

Table 7. **Known risks of atherectomy**

| **Event Category** | **Event** |
|---|---|
| | Paradoxical embolization |
| Local | Leg edema |
| | Leg pain |
| | Back pain |
| | Hemorrhage |
| Cerebrovascular | Transient ischemic attack |
| | Stroke |
| | Intracranial hemorrhage |
| Genitourinary | Urinary retention |
| | Urinary tract infection |
| | Renal stones |
| | Renal insufficiency, failure |
| | Hematuria |
| | Impotence and other disorders of sexual function |
| Pulmonary | Exacerbation of chronic lung disease |
| | Pneumonia |
| | Respiratory failure |
| | Bronchitis |
| | Bronchospasm |
| Gastrointestinal | Peptic ulcer disease |
| | Reflux esophagitis |
| | Nausea and vomiting |
| | Diarrhea |
| | Constipation |
| | Hepatitis |
| | Hepatic insufficiency |
| | Cholelithiasis / cholecystitis |
| Metabolic/systemic disorders | Electrolyte imbalances |
| | Hyperglycemia |
| | Hypoglycemia |

Table 7. **Known risks of atherectomy**

| Event Category | Event |
|---|---|
| | Fluid overload |
| | Dehydration |
| | Thrombocytopenia |
| | Leukopenia |
| | Anemia with or without need for transfusion |
| Miscellaneous | Sepsis |
| | Psychiatric disorders including depression |
| | Mental status changes |
| | Insomnia |
| | Embolization of device components |
| | Loss of device components within vascular tree |
| | Inability to extract device from vascular tree |
| | Allergic reactions to device components |
| | Allergic reactions to concomitant medications |

There are other health risks and discomforts associated with the testing that the subjects will undergo before and after their procedure, including, but not limited to, bruising during blood collection, pain and bruising at the access site and radiation exposure during imaging procedures.

## 15.2. Risk Mitigation

The Sponsor designed the Revolution™ Peripheral Atherectomy System and the clinical investigational protocol to minimize risks to the study participants. Study eligibility criteria were formulated to limit use of the study device to subjects and target lesions that fit the device specifications. Evaluation of safety data by an independent CEC and DSMB and assessment of angiograms by an external core laboratory will provide an ongoing assessment of safety-related events, both individually and in aggregate.

## 15.3. Benefit to Subjects

It is hoped that the Revolution™ Peripheral Atherectomy System will provide additional treatment options for minimally-invasive revascularization in subjects with symptomatic infrainguinal peripheral arterial occlusive disease. Debulking of atherosclerotic lower extremity lesions may improve the early and longer-term results of balloon angioplasty.[22,39] Atherectomy, in some cases, may improve blood flow as a sole intervention without the need for other adjunctive interventions or for implantation of a permanent metallic stent.[40,41]

### 15.4. Study Justification

This study is justified considering previous work showing positive outcomes obtained through combined use of atherectomy and angioplasty/stenting. This study will attempt to build on past results and, potentially, identify additional benefits of atherectomy use in patients with PAD.

## 16. ABBREVIATIONS

Abbreviations contained throughout this document are listed in **Table 8**:

**Table 8. Abbreviations**

| | |
|---|---|
| ABI | Ankle-Brachial Index |
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| CEC | Clinical Events Committee |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| DSMB | Data Safety Monitoring Board |
| FDA | US Food and Drug Administration |
| IFU | Instructions for Use |
| IRB | Institutional Review Board |
| ITT | Intention to Treat |
| IUD | Intrauterine Device |
| LCL | Lower Confidence Limit |
| MAE | Major Adverse Event |
| MLD | Minimum Luminal Diameter |
| PAD | Peripheral Arterial Disease |
| PG | Performance Goal |
| PP | Per Protocol |
| PTA | Percutaneous Transluminal Angioplasty |
| QVA | Quantitative Vascular Angiography |
| RVD | Reference Vessel Diameter |
| SADE | Serious Adverse Device Effect |
| SFA | Superficial Femoral Artery |

| | |
|---|---|
| TBI | Toe-Brachial Index |
| TLR | Target Lesion Revascularization |
| TVR | Target Vessel Revascularization |
| UADE | Unanticipated Adverse Device Effect |

## 17. ELECTRONIC DATA

Electronic data will only be accessible to authorized personnel through the use of a unique user identifier and password. Passwords are set to expire periodically. Access to electronic study data will be provided to research personnel upon completion of training. Read and write access will be provided to investigational sites but only for information and subject data at their own site. The CRO will have read-only access and can post queries for potential data-related discrepancies.

## 18. DEFINITIONS

Relevant definitions are included below in **Table 9:**

**Table 9. Definitions**

| **Rutherford Categories[42]** | | |
|---|---|---|
| # | *Clinical description* | *Objective criteria* |
| **0** | Asymptomatic – no hemodynamically significant occlusive disease | Normal treadmill or reactive hyperemia test |
| **1** | Mild claudication | Completes treadmill exercise*; AP after exercise > 50 mmHg but at least 20 mmHg lower than resting value |
| **2** | Moderate claudication | Between categories 1 and 3 |
| **3** | Severe claudication | Cannot complete standard treadmill exercise* *and* AP after exercise < 50 mmHg |
| **4** | Ischemic rest pain | Resting AP < 40 mmHg, flat or barely pulsatile ankle or metatarsal PVR; TP < 30 mmHg |
| **5** | Minor tissue loss – nonhealing ulcer, focal gangrene with diffuse pedal ischemia | Resting AP < 60 mmHg, ankle or metatarsal PVR flat or barely pulsatile; TP < 40 mmHg |
| **6** | Major tissue loss – extending above TM level, functional foot no longer salvageable | Same as category 5 |
| **Dissection Types[43]** | | |
| **A** | Minor radiolucent areas | |
| **B** | Dissections are parallel tracts | |
| **C** | Contrast outside the lumen | |
| **D** | Spiral luminal filling defects | |
| **E** | Persistent filling defects | |
| **F** | Total occlusion without distal antegrade flow | |
| ***5 minutes at 2 mph on a 12% incline** | | |

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# APPENDIX A. WALKING IMPAIRMENT QUESTIONNAIRE (WIQ)

***1. <u>WALKING IMPAIRMENT</u>:*** These questions ask about the reasons why you had difficulty walking. We would like to know how much difficulty you had walking during the last week. By difficulty, we mean how hard it was or how much physical effort it took to walk because of each of these problems.

| **A. PAD SPECIFIC QUESTIONS** | **LEG** | **DEGREE OF DIFFICULTY** | | | | |
|---|---|---|---|---|---|---|
| | | **None** | **Slight** | **Some** | **Much** | **Very** |
| 1. Pain, aching, or cramps in your calves? (or buttocks) | Right | 4 | 3 | 2 | 1 | 0 |
| | Left | 4 | 3 | 2 | 1 | 0 |
| | Both | 4 | 3 | 2 | 1 | 0 |

| **B. DIFFERENTIAL DIAGNOSIS** | **DEGREE OF DIFFICULTY** | | | | |
|---|---|---|---|---|---|
| | **None** | **Slight** | **Some** | **Much** | **Very** |
| 1. Pain, stiffness, or aching in your joints (ankles, knees, or hips)? | 4 | 3 | 2 | 1 | 0 |
| 2. Weakness in one or both of your legs? | 4 | 3 | 2 | 1 | 0 |
| 3. Pain or discomfort in your chest? | 4 | 3 | 2 | 1 | 0 |
| 4. Shortness of breath? | 4 | 3 | 2 | 1 | 0 |
| 5. Heart Palpitations? | 4 | 3 | 2 | 1 | 0 |
| 6. Other Problems? (Please list) | | | | | |
| a. | 4 | 3 | 2 | 1 | 0 |
| b. | 4 | 3 | 2 | 1 | 0 |
| c. | 4 | 3 | 2 | 1 | 0 |

**2. <u>WALKING DISTANCE</u>**: Report the degree of physical difficulty that best describes how hard it was for you to walk on level ground without stopping to rest for each of the following distances during the last week:

| **DISTANCE** | **DEGREE OF DIFFICULTY** | | | | |
|---|---|---|---|---|---|
| | **None** | **Slight** | **Some** | **Much** | **Very** |
| 1. Walking indoors such as around your home? | 4 | 3 | 2 | 1 | 0 |
| 2. Walking 15 meters or 50 feet? | 4 | 3 | 2 | 1 | 0 |
| 3. Walking 45 meters or 150 feet (1/2 block)? | 4 | 3 | 2 | 1 | 0 |
| 4. Walking 90 meters or 300 feet (1 block)? | 4 | 3 | 2 | 1 | 0 |
| 5. Walking 180 meters or 600 feet (2 blocks)? | 4 | 3 | 2 | 1 | 0 |
| 6. Walking 270 meters or 900 feet (3 blocks)? | 4 | 3 | 2 | 1 | 0 |
| 7. Walking 450 meters or 1500 feet (5 blocks)? | 4 | 3 | 2 | 1 | 0 |

**3. <u>WALKING SPEED</u>**: Report the degree of physical difficulty that best describes how hard it was for you to walk one city block on level ground at each of these speeds without stopping to rest during the last week:

| **SPEED** | **DEGREE OF DIFFICULTY** | | | | |
|---|---|---|---|---|---|
| | **None** | **Slight** | **Some** | **Much** | **Very** |
| 1. Walking 1 block slowly? | 4 | 3 | 2 | 1 | 0 |
| 2. Walking 1 block at an average speed? | 4 | 3 | 2 | 1 | 0 |
| 3. Walking 1 block quickly? | 4 | 3 | 2 | 1 | 0 |
| 4. Running or jogging one block? | 4 | 3 | 2 | 1 | 0 |

**4. <u>STAIR CLIMBING</u>**: Report the degree of physical difficulty that best describes how hard it was for you to climb stairs for each of these questions without stopping to rest during the past week:

| **STAIRS** | **DEGREE OF DIFFICULTY** | | | | |
|---|---|---|---|---|---|
| | **None** | **Slight** | **Some** | **Much** | **Very** |
| 1. Climbing 1 flight of stairs | 4 | 3 | 2 | 1 | 0 |
| 2. Climbing 2 flights of stairs | 4 | 3 | 2 | 1 | 0 |
| 3. Climbing 3 flights of stairs | 4 | 3 | 2 | 1 | 0 |

## APPENDIX B. VASCULAR QUALITY OF LIFE (VASCUQOL-6)

1. Because of the poor circulation in my legs, the range of activities that I would have liked to do in the past two weeks has been…

    1. Severely limited - most activities not done…
    2. Very limited
    3. Very slightly limited
    4. Not limited at all - have done all the activities that I wanted to

2. During the past two weeks, my legs felt tired or weak...

    1. All of the time
    2. Some of the time
    3. A little of the time
    4. None of the time

3. During the past two weeks, because of the poor circulation in my legs, my ability to walk has been…

    1. Totally limited, couldn't walk at all
    2. Very limited
    3. A little limited
    4. Not at all limited

4. During the past two weeks, I have been concerned about having poor circulation in my legs...

    1. All of the time
    2. Some of the time
    3. A little of the time
    4. None of the time

5. During the past two weeks, because of the poor circulation in my legs, my ability to participate in social activities has been…

1. Totally limited, couldn't socialize at all
2. Very limited
3. A little limited
4. Not at all limited

6. During the past two weeks, when I have had pain in the leg (or foot) it has given me…

1. A great deal of discomfort or distress
2. A moderate amount of discomfort or distress
3. Very little discomfort or distress
4. No discomfort or distress

## SIGNATURE APPROVAL PAGE

Revolution™ Peripheral Atherectomy System for Lower Extremity Peripheral Arterial Revascularization

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