Prospective, multi-center, single-arm study of the Shockwave Medical M^{5+} Peripheral Intravascular Lithotripsy (IVL) System in calcified peripheral arteries (Disrupt PAD^{+})

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SHOCKWAVE MEDICAL INC

Prospective, multi-center, single-arm study of the Shockwave Medical M^{5+} Peripheral Intravascular Lithotripsy (IVL) System in calcified peripheral arteries (Disrupt PAD+)

Protocol Number: CP 64007

Protocol Date: 22 April 2021

Revision: D

Study Device: Shockwave Medical M^{5+} Peripheral Intravascular Lithotripsy System

Study Sponsor Name and Address: Shockwave Medical, Inc.
5403 Betsy Ross Drive
Santa Clara, CA 95054
USA

CONFIDENTIAL

THIS STUDY PROTOCOL CONTAINS CONFIDENTIAL INFORMATION FOR USE BY THE INVESTIGATORS AND THEIR DESIGNATED REPRESENTATIVES PARTICIPATING IN THE EVALUATION OF THE PROSPECTIVE, MULTI-CENTER, SINGLE-ARM STUDY OF THE SHOCKWAVE MEDICAL M^{5+} PERIPHERAL INTRAVASCULAR LITHOTRIPSY (IVL) SYSTEM IN CALCIFIED PERIPHERAL ARTERIES (DISRUPT PAD+). IT SHOULD BE HELD CONFIDENTIAL AND MAINTAINED IN A SECURE LOCATION. IT SHOULD NOT BE COPIED OR MADE AVAILABLE FOR REVIEW BY ANY UNAUTHORIZED PERSON OR FIRM WITHOUT WRITTEN PERMISSION FROM SHOCKWAVE MEDICAL, INC.

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1.0 INVESTIGATOR SIGNATURE PAGE

Study Title: Prospective, multi-center, single-arm study of the Shockwave Medical M^{5+} Peripheral Intravascular Lithotripsy (IVL) System in calcified peripheral arteries

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USA

Principal Investigator Acknowledgement Signature

I have received and reviewed this version of the above noted study protocol and will conduct the study in accordance with the outlined protocol requirements, all attachments, and applicable local and Food and Drug Administration regulations. This investigation will be conducted in accordance with the ethical principles as noted in the Declaration of Helsinki and with the ICH/Good Clinical Practices, and applicable IRB/EC requirements.

_____
Principal Investigator's Name (print)

_____ _____
Principal Investigator's Signature Date

2.0 STUDY SUMMARY

Study Title:	Prospective, multi-center, single-arm study of the Shockwave Medical M5+ Peripheral Intravascular Lithotripsy (IVL) System in calcified peripheral arteries (Disrupt PAD+)
Study Objective:	The objective of this study is to assess the safety and performance of the Shockwave M5+ Peripheral IVL System to treat calcified peripheral arteries in pre-market countries, and to assess continued safety and effectiveness in the US.
Study Device(s):	Shockwave Medical M5+ Peripheral IVL System
Indications for Use:	The Shockwave Medical M5+ Peripheral IVL System is indicated for lithotripsy-enhanced, low-pressure balloon dilatation of lesions, including calcified lesions, in the peripheral vasculature, including the iliac, femoral, ilio-femoral, popliteal, infra-popliteal, and renal arteries. This device is not intended for use in coronary, carotid, or cerebrovascular arteries.
Study Design:	Prospective, multi-center, single-arm study of the M5+ Peripheral IVL system to treat calcified peripheral arteries.
Enrollment:	A minimum of 40 lesions in up to 40 subjects at up to 10 sites in Australia, New Zealand and the US will be enrolled with the aim of treating at least 20 target lesions with the 8.0 mm IVL catheter. A maximum of three target lesions may be treated per subject.
Subject Population:	Subjects with moderate and severely calcified iliac and femoropopliteal artery disease presenting with Rutherford Category 2 to 5.
Study Duration / Follow-Up Period:	Approximately 6 months of enrollment at up to 10 sites in Australia, New Zealand and the US. Study subjects will be followed through discharge, 30 days, 6 and 12 months. Duplex Ultrasound (DUS) assessments will be completed at 12 months. Total anticipated study duration is 18 months.
Primary Safety Endpoint	Major Adverse Events (MAE) at 30 days defined as: • Need for emergency surgical revascularization of target limb • Unplanned target limb major amputation (above the ankle)

	• Symptomatic thrombus or distal emboli that require surgical, mechanical or pharmacologic means to improve flow and extend hospitalization • Perforations that require an intervention, including bail-out stenting
Primary Performance Endpoint:	• Technical success defined as final residual stenosis ≤30% without flow-limiting dissection (≥ Grade D) of the lesion by angiographic core lab
Secondary Endpoints:	• IVL Technical success defined as residual stenosis ≤30% without flow-limiting dissection (≥ Grade D) of the lesion post-IVL by angiographic core lab • Procedural success defined as final residual stenosis ≤30% without any flow-limiting dissection (≥ Grade D) in all target lesions by angiographic core lab • Major Adverse Events (MAE) at 6 and 12 months • Primary patency at 12 months defined as freedom from clinically-driven target lesion revascularization (TLR) and freedom from restenosis determined by duplex ultrasound or angiogram ≥50% stenosis • Clinically-driven target lesion revascularization (TLR) at 30 days, 6 and 12 months • Ankle-brachial index (ABI) at 12 months, reported as change from baseline • Rutherford Category at 30 days, 6 and 12 months, reported as change from baseline
Study Inclusion Criteria:	**General Inclusion Criteria** 1. Subject is able and willing to comply with all assessments in the study. 2. Subject or subject's legal representative have been informed of the nature of the study, agrees to participate and has signed the approved consent form. 3. Age of subject is > 18. 4. Rutherford Clinical Category 2, 3, 4 or 5 of the target limb(s). 5. Estimated life expectancy >1 year.

	6. Subject is intended to undergo treatment with Shockwave M5+ Peripheral IVL System for de novo lesions of the ilio-femoropopliteal arteries. **Angiographic Inclusion Criteria** 7. Single or multiple de novo target lesion(s) located from the common iliac to the femoropopliteal artery, in one or both limbs. 8. Target lesion reference vessel diameter is between 3.5mm and 10.0mm by visual estimate. 9. Target lesion is ≥70% stenosis by investigator via visual estimate. 10. Target lesion length is ≤200mm for lesions 70-99% stenosed. Target lesion can be all or part of the 200mm treated zone. 11. Chronic total occlusion, lesion length is ≤100mm of the total ≤200 mm target lesion. 12. Subject has at least one patent tibial vessel on the target leg with runoff to the foot, defined as no stenosis >50%. 13. Calcification is at least moderate defined as presence of fluoroscopic evidence of calcification: 1) on parallel sides of the vessel and 2) extending > 50% the length of the lesion if lesion is ≥50mm in length; or extending for minimum of 20mm if lesion is <50mm in length.
Study Exclusion Criteria:	**General Exclusion Criteria** 1. Rutherford Clinical Category 0, 1, and 6. 2. Subject has active infection requiring antibiotic therapy. 3. History of endovascular or surgical procedure on the target limb within the last 30 days or planned within 30 days of the index procedure. *Note: Concomitant IVL treatment to facilitate large bore access at the time of procedure is allowed.* 4. Subject in whom antiplatelet or anticoagulant therapy is contraindicated. 5. Subject has known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-treated. 6. Subject has known allergy to urethane, nylon, or silicone. 7. Myocardial infarction within 60 days prior to enrollment. 8. History of stroke within 60 days prior to enrollment.

	9. Subject has acute or chronic renal disease defined as serum creatinine of >2.5 mg/dL or >220 umol/L, unless on dialysis. 10. Subject is pregnant or nursing. 11. Subject is participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint. 12. Subject has other medical, social or psychological problems that, in the opinion of the investigator, preclude them from receiving this treatment, and the procedures and evaluations pre- and post-treatment. 13. The planned use of specialty balloons, re-entry or atherectomy devices in the target lesion(s). **Angiographic Exclusion Criteria** 14. In-stent restenosis within 10mm of the target zone. 15. Target lesions distal to the popliteal artery. 16. Evidence of aneurysm or thrombus in target vessel. 17. No calcium or mild calcium in the target lesion. 18. Target lesion within native or synthetic vessel grafts. 19. Subject has more than three target lesions requiring treatment. 20. Subject has significant non-target lesion (>50% stenosis or occlusion) within the target limb (e.g. iliac, common femoral or below-the-knee) not successfully treated prior to treatment of the target lesions. 21. Failure to successfully cross the guidewire across the target lesion; successful crossing defined as tip of the guidewire distal to the target lesion in the absence of flow limiting dissections or perforations.
Study Statistical Methods:	Descriptive statistics will be reported.
Study Sponsor/Study Management Contact:	Shockwave Medical, Inc. 5403 Betsy Ross Drive Santa Clara, CA 95054 USA Contact: Lahn Fendelander Title: Senior Director, Clinical Affairs Telephone: (direct): (339) 927-3402 Email: lfendelander@shockwavemedical.com

3.0 INTRODUCTION

3.1 Background

Peripheral arterial disease (PAD) is one of the most common indications of atherosclerotic disease and impacts greater than 200 million people globally (Madhavan et al., 2020). PAD is caused by the accumulation of plaque in the arteries that do not supply the brain or the heart. The reduced blood flow may lead to pain, tissue loss and eventual foot/leg amputation or death. When the disease manifests in the peripheral arteries, it is usually indicative of a developing system-wide problem with atherosclerosis. If left untreated, PAD may significantly elevate the risk of cardiovascular disease morbidity and mortality (Davros, Garra, & Zeman, 1991).

Although it can involve the renal arteries and/or the arteries of the neck or arms, PAD normally develops in the lower extremities. Risk factors for PAD include hypertension, hypercholesterolemia, diabetes and smoking (Davros et al., 1991). Individuals with PAD are at risk for short-term cardiovascular ischemic events and can develop nonhealing wounds, gangrene, or may even need amputation in the affected limb (Bashir & Cooper, 2003; Davros et al., 1991). Diabetes and kidney disease can also cause clinical complications in individuals with PAD and can lead to a greater risk of limb amputations (Davros et al., 1991). The early diagnosis and treatment of PAD reduces an individual's risk of cardio- or cerebrovascular disease morbidity and mortality.

Percutaneous endovascular therapies are being increasingly employed as the primary revascularization treatment for disease of the superficial femoral artery and/or popliteal arteries, including calcified occlusions (Diamantopoulos & Katsanos, 2014; Jaff et al., 2015; Norgren et al., 2007; Roberts et al., 2014). Endovascular therapies include percutaneous angioplasty (PTA), nitinol stents, directional and rotational atherectomy, laser atherectomy, drug-eluting stents (DES) and drug-coated balloons (DCB) (Norgren et al., 2007).

Unmet needs in the management of PAD are driving the demand for new plaque modification tools, including Shockwave Medical's Peripheral Intravascular Lithotripsy (IVL). Intravascular Lithotripsy is a balloon-based technology that targets calcification to "normalize" vessel compliance prior to low pressure dilatation. Peripheral IVL is designed to optimize acute gain while minimizing acute vessel injury and reducing bail-out stenting. Pooled 30-day study results of the Disrupt PAD I and PAD II studies demonstrated compelling effectiveness and safety results of IVL in the treatment of moderately and severely calcified vessels with minimal vessel injury and only one stent implanted in 95 subjects. Acute effectiveness results showed high procedural success across all types of lesions and a large acute gain of 3.0mm after the procedure (Zeller, 2016). The PAD II 12-month results identified that optimal technique (with at least 1.1:1 IVL balloon to artery sizing and adequate therapeutic coverage) improves 12-month primary patency, resulting in a clinically-driven TLR rate of 8.6% without concomitant DCB or DES (Brodmann, Holden, & Zeller, 2018).

The Disrupt PAD III randomized trial is underway and will compare the optimal vessel preparation strategy prior to DCB in calcified femoropopliteal arteries. An interim analysis of the initial 200 patients treated in the PAD III Observational Study demonstrated consistent acute safety and

effectiveness outcomes in a real-world population in a variety of calcified peripheral arteries and higher disease complexity (Adams et al., 2020). In addition, an interim analysis of IVL treatment in calcified iliac lesions in the PAD III Observational Study demonstrated IVL is safe and effective for the treatment of calcified iliac arteries and optimizes large-bore access (Armstrong et al., 2020).

3.2 Study Rationale

The Shockwave Medical M^5 Peripheral IVL Catheter has FDA clearance and CE Mark approval and is indicated for lithotripsy-enhanced, low pressure balloon dilatation of calcified, stenotic peripheral arteries in patients who are candidates for percutaneous therapy. In an effort to continually optimize IVL therapy, the M^{5+} Peripheral IVL System represents an iterative catheter design change relative to the M5 device which (1) introduces a larger balloon size (8.0 mm), (2) extends the catheter working length from 110 cm to 135 cm, and (3) increases the frequency of IVL pulse delivery from 1 Hz (1 pulse per second) to 2 Hz (1 pulse per 0.5 seconds for all catheter sizes) with the goal of reducing overall procedure time. The objective of this study is to assess the safety and performance of the Shockwave M^{5+} Peripheral IVL System to treat calcified peripheral arteries in pre-market countries, and to assess continued safety and effectiveness in the US. It is being conducted as a post-market study in the US following FDA clearance of the M^{5+} catheter and as a pre-market study in Australia and New Zealand.

4.0 STUDY DEVICE / TEST ARTICLE DESCRIPTION

4.1 Device/Test Article Description

The Shockwave Medical M5+ Peripheral IVL Catheter is a proprietary lithotripsy device delivered through the peripheral arterial system of the lower extremities to the site of an otherwise difficult to treat calcified stenosis. Energizing the lithotripsy device will generate pulsatile mechanical energy within the target treatment site, disrupting calcium within the lesion and allowing subsequent dilation of a peripheral artery stenosis using low balloon pressure. The IVL Catheter is comprised of an integrated balloon with an array of integrated lithotripsy emitters for the localized delivery of pulsatile mechanical energy. The system consists of the IVL Catheter, an IVL Connector Cable and an IVL Generator.

The M5+ IVL Catheter is available in nine (9) sizes: 3.5 x 60mm, 4.0 x 60mm, 4.5 x 60mm, 5.0 x 60mm, 5.5 x 60mm, 6.0 x 60mm, 6.5 x 60mm, 7.0 x 60mm, and 8.0 x 60mm. The M5+ Peripheral IVL Catheter is compatible with a 6 or 7 F sheath and has a working length of 135cm.

The Shockwave M5+ Peripheral IVL Catheter shaft contains an inflation lumen, a guidewire lumen, and the lithotripsy emitters. The inflation lumen is used for inflation and deflation of the balloon with 50/50 saline/contrast medium. The guidewire lumen enables the use of a 0.014" guidewire to facilitate advancement of the catheter to and through the target stenosis. The system is designed as 'Over-the-wire' (OTW) with 135cm shaft working length, so an exchange length (300cm) guidewire is indicated. The emitters are positioned within the balloon working length for delivery of pulsatile mechanical energy. The balloon is located near the distal tip of the catheter. Two radiopaque marker bands within the balloon denote the length of the balloon to aid in positioning of the balloon during treatment. The balloon is designed to provide an expandable segment of known length and diameter at a specific pressure. The proximal hub has one port each for inflation/deflation of the balloon, guidewire lumen, and connection to the IVL Connector Cable.

The IVL Catheter is supplied sterile via E-beam sterilization. It is intended for single use only and is not intended for reuse or re-sterilization. The Connector Cable and IVL Generator are non-sterile, reusable medical devices.

Refer to the Instructions for Use (IFU) provided for a complete product description.

4.2 Indication for Use

The Shockwave Medical M5+ Peripheral IVL System is indicated for lithotripsy-enhanced, low-pressure balloon dilatation of lesions, including calcified lesions, in the peripheral vasculature, including the iliac, femoral, ilio-femoral, popliteal, infra-popliteal, and renal arteries. This device is not intended for use in coronary, carotid, or cerebrovascular arteries.

5.0 STUDY OBJECTIVES

The objective of this study is to assess the safety and performance of the Shockwave M^{5+} Peripheral IVL System to treat calcified peripheral arteries in pre-market countries, and to assess continued safety and effectiveness in the US.

5.1 Primary Endpoint(s)

Primary Safety Endpoint

Major Adverse Events (MAE) at 30 days defined as:

- Need for emergency surgical revascularization of target limb
- Unplanned target limb major amputation (above the ankle)
- Symptomatic thrombus or distal emboli that require surgical, mechanical or pharmacologic means to improve flow and extend hospitalization
- Perforations that require an intervention, including bail-out stenting

Primary Performance Endpoint(s)

Technical success is defined as final residual stenosis ≤30% without flow-limiting dissection (≥ Grade D) of the lesion by angiographic core lab.

5.2 Secondary Endpoint(s)

Performance

- IVL Technical success is defined as residual stenosis ≤30% without flow-limiting dissection (≥ Grade D) of the lesion post-IVL by angiographic core lab.
- Procedural success is defined as final residual stenosis ≤30% without any flow-limiting dissection (≥ Grade D) in all target lesions by angiographic core lab.

Safety

- MAE at 6 and 12 months

Patency

- Primary patency at 12 months defined as freedom from clinically-driven target lesion revascularization (TLR) and freedom from restenosis determined by duplex ultrasound or angiogram ≥50% stenosis. Acute PTA failure requiring a stent of the target lesion at any time during the index procedure will be counted as a loss of primary patency.
- Clinically driven target lesion revascularization (TLR) at 30 days, 6 and 12 months

Clinical

- Ankle-brachial index (ABI) at 12 months, reported as change from baseline
- Rutherford Category at 30 days, 6 and 12 months, reported as change from baseline

6.0 STUDY DESIGN

The Disrupt PAD+ study is a prospective, multi-center, single-arm study of the M^{5+} Peripheral IVL System to treat calcified peripheral arteries.

6.1 Site Selection

Up to 10 sites located in Australia, New Zealand and the US will participate in the study.

6.2 Number of Subjects

A minimum of 40 lesions in up to 40 subjects with moderate and severely calcified iliac and femoropopliteal artery disease presenting with Rutherford Category 2 to 5 will be enrolled. Each site will be allowed to enroll a maximum of 12 subjects. Multiple lesion treatment with IVL will be allowed and a minimum of twenty (20) lesions across all enrolled subjects must be treated with the 8.0 mm catheter size.

6.3 Clinical Study Duration

Enrollment is anticipated to last approximately 6 months. Study subjects will be followed through hospital discharge, 30 days, and 6 and 12 months post-procedure. Duplex ultrasound (DUS) assessments will be completed at 12 months. Total anticipated study duration is 18 months.

7.0 STUDY PROCEDURES

7.1 Screening

Patients presenting to the institution with known iliac and/or femoropopliteal disease requiring an interventional procedure will be evaluated for eligibility and participation in the study. A member of the participating site's study team will perform an initial evaluation of the potential participant's medical history and previously performed examinations to assess for initial eligibility. Pre-procedure imaging (DUS, angiogram, CTA, MRA) should be performed according to the institution's standard of care.

Potential subjects will be screened for eligibility. Written informed consent will be obtained prior to any study-specific requirements. A potential subject will be informed of the elements of the study including risks, potential benefits, and required follow-up procedures prior to obtaining the potential subject's informed consent.

Subjects who meet the clinical inclusion/exclusion criteria will undergo an angiogram. At the time of the angiogram, the subject is considered enrolled if all angiographic eligibility criteria are met, and the M^{5+} peripheral IVL catheter is inserted into the patient. A subject is considered an angiographic screen failure if they do not meet angiographic eligibility. Patients who screen failed will be documented as such in the electronic data capture (EDC) system.

7.2 Subject Selection

7.2.1 Inclusion Criteria

General Inclusion Criteria

1. Subject is able and willing to comply with all assessments in the study.

2. Subject or subject's legal representative have been informed of the nature of the study, agrees to participate and has signed the approved consent form.

3. Age of subject is > 18.

4. Rutherford Clinical Category 2, 3, 4 or 5 of the target limb(s).

5. Estimated life expectancy >1 year.

6. Subject is intended to undergo treatment with Shockwave M^{5+}Peripheral IVL System for de novo lesions of the ilio-femoropopliteal arteries.

Angiographic Inclusion Criteria

7. Single or multiple de novo target lesion(s) located from the common iliac to the femoropopliteal artery, in one or both limbs.

8. Target lesion reference vessel diameter is between 3.5mm and 10.0mm by visual estimate.

9. Target lesion is ≥70% stenosis by investigator via visual estimate.

10. Target lesion length is ≤200mm for lesions 70-99% stenosed. Target lesion can be all or part of the 200mm treated zone.

11. Chronic total occlusion, lesion length is ≤100mm of the total ≤200 mm target lesion.

12. Subject has at least one patent tibial vessel on the target leg with runoff to the foot, defined as no stenosis >50%.

13. Calcification is at least moderate defined as presence of fluoroscopic evidence of calcification: 1) on parallel sides of the vessel and 2) extending > 50% the length of the lesion if lesion is ≥50mm in length; or extending for minimum of 20mm if lesion is <50mm in length.

7.2.2 Exclusion Criteria

General Exclusion Criteria

1. Rutherford Clinical Category 0, 1 and 6.

2. Subject has active infection requiring antibiotic therapy.

3. History of endovascular or surgical procedure on the target limb within the last 30 days or planned within 30 days of the index procedure. *Note: Concomitant IVL treatment to facilitate large bore access at the time of procedure is allowed.*

4. Subject in whom antiplatelet or anticoagulant therapy is contraindicated.

5. Subject has known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-treated.

6. Subject has known allergy to urethane, nylon, or silicone.

7. Myocardial infarction within 60 days prior to enrollment.

8. History of stroke within 60 days prior to enrollment.

9. Subject has acute or chronic renal disease defined as serum creatinine of >2.5 mg/dL or >220 umol/L, unless on dialysis.

10. Subject is pregnant or nursing.

11. Subject is participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint.

12. Subject has other medical, social or psychological problems that, in the opinion of the investigator, preclude them from receiving this treatment, and the procedures and evaluations pre- and post-treatment.

13. The planned use of specialty balloons, re-entry or atherectomy devices in the target lesion(s).

Angiographic Exclusion Criteria

14. In-stent restenosis within 10mm of the target zone.

15. Target lesions distal to the popliteal artery.

16. Evidence of aneurysm or thrombus in target vessel.

17. No calcium or mild calcium in the target lesion.

18. Target lesion within native or synthetic vessel grafts.

19. Subject has more than three target lesions requiring treatment.

20. Subject has significant non-target lesion (>50% stenosis or occlusion) within the target limb (e.g. iliac, common femoral or below-the-knee) not successfully treated prior to treatment of the target lesions.

21. Failure to successfully cross the guidewire across the target lesion; successful crossing defined as tip of the guidewire distal to the target lesion in the absence of flow limiting dissections or perforations.

7.3 Informed Consent

Prior to undergoing any study-specific tests or procedures, the subject or their legally authorized representative must sign and date the site's current and approved Institutional Review Board (IRB)/Ethics Committee (EC) informed consent form (ICF) in order to be eligible for study participation. The informed consent must contain all elements required by 21 CFR Part 50 and ISO 14155:2011/ AC: 2011 and comply with the ethical principles of the Declaration of Helsinki.

7.3.1 Process for Obtaining Informed Consent

The process for obtaining informed consent is outlined below:

- The Investigator or his/her authorized designee conducts the informed consent process,
- All aspects of the clinical study that are relevant to the subject's decision to participate will be included in the consent form,
- Investigators will avoid any coercion or undue improper influence on, or inducement of, the subject to participate,
- The consent process shall not waive or appear to waive the subject's legal rights,
- The consent must use native non-technical language that is understandable to the subject,
- The Investigator or designee will provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation,
- The consent must include personally dated signatures of the subject and the Investigator, or an authorized designee responsible for conducting the informed consent process, and/or all signatures required by the reviewing IRB/EC,
- The Investigator or designee will provide the subject with a copy of the signed and dated informed consent form and any other written information.

7.3.2 Subjects Needing Legally Authorized Representative

Informed consent may be given by a legally authorized representative only if a subject is unable to make the decision to participate in a clinical study. In such cases, the subject shall also be informed about the clinical study within his/her ability to understand.

Please follow the local IRB/EC guidelines on this process.

7.3.3 Subjects Unable to Read or Write

Informed consent shall be obtained through a supervised oral process if a subject or legally authorized representative is unable to read or write, if allowed by the IRB/EC. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be explained to the prospective subject or his/her legally authorized representative and, whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained and that informed consent was freely given.

7.3.4 Addition of New Information

Shockwave Medical will revise the written informed consent form whenever new information becomes available that may be relevant to the subject's confirmed participation in the study. The revised information will be sent to the Investigator for approval by the IRB/EC. After approval by the IRB/EC, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

Please follow the local IRB/EC guidelines on the process of re-consenting subjects.

7.4 Schedule of Events and Evaluations

Table 1 lists the schedule of events and evaluations required for the study.

Table 1. Study Schedule of Events

	Screening/ Baseline[2]	Enrollment and Procedure	Discharge[3]	30 Days[4] (+/- 7 days)	6 Months[4] (+/- 30 days)	12 Months (+/- 30 days)	Pre-Target Limb Revasc
Informed Consent	X[1]						
Medical History	X						
Physical Examination	X		X	X	X	X	X
Baseline labs	X						
Pregnancy test	X						
Ankle Brachial Index (ABI)	X			X[5]	X[5]	X	X
Rutherford Category (RC)	X			X	X	X	X
Angiographic Lesion Assessment		X					X
IVL Procedure		X					
Duplex Ultrasound						X	
Medication regimen per protocol			X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X
OCT or IVUS (optional)		X					

[1] Consent to be obtained within 30 days prior to procedure.
[2] Evaluations may be done up to 30 days before the procedure with the exception of ABI, which may be completed within 60 days of the procedure.
[3] Examinations are to be completed within 12-24 hours post-procedure or prior to discharge, whichever comes first.
[4] 30-Day and 6-month visit can be conducted as an on-site or remote visit.
[5] ABI should be assessed if visit is conducted on-site.

7.5 Medications

Anticoagulation/antiplatelet medications will be administered according to the 2017 European Society of Cardiology (ESC) and European Society of Vascular Surgery (ESVS) PAD guidelines (Aboyans et al., 2018) and the 2016 American College of Cardiology (ACC) and American Heart Association (AHA) PAD guidelines (Gerhard-Herman et al., 2017).

Additional recommendations for anticoagulation and antiplatelet medications include:

- Unfractionated heparin dosing should be undertaken according to hospital standard of care.
- Prasugrel or ticagrelor may be used as an alternative to clopidogrel for existing management of acute coronary syndrome (ACS).
- Follow antiplatelet and anticoagulation guidelines for the management of patients with atrial fibrillation.

7.6 Screening/Baseline Procedures

Baseline assessments must be completed within 30 days of the procedure with the exception of ABI, which can be completed within 60 days of the procedure, and a pregnancy test, which must be done within 7 days of procedure. Informed consent must be obtained prior to any study-specific evaluations needed to assess eligibility which are not considered standard of care. Subjects on warfarin or direct thrombin inhibitors should be followed per institutional standard of care by the physician.

Baseline assessments include:

- Medical history
- Physical examination
  - Vital signs
  - Height and weight
- Ankle-brachial index
- Rutherford Category
- Laboratory assessments
- Urine pregnancy test if female of child-bearing age

7.7 Index Procedure

7.7.1 Definition of Enrollment

The definition of enrollment is when the subject signs informed consent, meets all inclusion criteria, none of the exclusion criteria, and the IVL catheter has been inserted over a 0.014" guidewire which had been previously passed across the study lesion.

7.7.2 Index Procedure

Non-target lesions within a limb should be treated successfully prior to treatment of any target lesions. Non-target lesions may be treated with any commercially available device; treating a non-target lesion with a device that is unapproved or considered investigational will result in a protocol deviation.

A full description of the procedure is detailed in the Instructions for Use (IFU). The appropriately sized IVL balloon catheter should be selected per the IFU (select a balloon catheter size that is 1.1:1 based on balloon compliance chart and reference vessel diameter; the largest diameter

balloon should be used if 1.1:1 sizing is not available). Once the IVL balloon is placed in the target lesion area, the balloon should be inflated to 4 atm and IVL treatment delivered for the pre-programmed time of 15 seconds to deliver 30 pulses. Note that the generator is programmed to force a minimum pause time of 10 seconds following every 30 pulses delivered. **Table 2** lists the pulsing sequence for IVL treatment.

Table 2: IVL System Sequence Chart

Treatment Frequency	2 Hz (1 Pulse every 0.5 Seconds)
Maximum Number of Continuous Pulses (1 cycle)	30 Pulses
Minimum Pause Time	10 Seconds
Maximum Total Pulses Per Catheter (10 cycles)	Displayed on generator

If the operator is unable to pass the IVL balloon through the lesion, a standard PTA balloon up to 3.0mm may be used for pre-dilatation prior to treatment with the IVL Balloon. All efforts should be made to pass the IVL balloon prior to use of a standard PTA balloon.

Following delivery of the first IVL cycle (30 pulses), inflate the balloon to the reference size using the Balloon Compliance Chart (refer to IFU) and record lesion response on fluoroscopy. Deflate the balloon and wait 10 seconds to re-establish blood flow. Repeat the steps above to complete a second delivery cycle of 30 pulses to complete a single treatment consisting of 60 pulses. Additional treatment cycles can be performed if deemed necessary.

If an additional lesion area needs to be treated, follow the treatment steps as identified per the IFU. The catheter can be advanced to the next treatment area. Confirm the balloon catheter is of the appropriate size for the next treatment area.

Post-dilatation with a semi or non-compliant PTA balloon catheter should be completed when post-IVL results in one of the following below. The physician should use a 1:1 balloon catheter to artery ratio and may dilate for up to three minutes.

- Residual stenosis ≥30% by visual estimate, or
- Presence of a flow-limiting (≥Grade D) dissection, or
- Trans-lesional gradient >10 mm Hg is observed.

Follow the angiographic core lab guidelines to complete angiography showing all target lesions with reproducible landmarks for follow-up evaluation and assessment.

Any commercially approved drug-coated balloon may be used after IVL. Provisional stenting should be performed with a bare metal or drug-eluting stent after primary treatment or post-dilatation balloon inflations are determined not to be successful. The angiographic core lab will confirm correct use of a stent based on the criteria above for subjects that receive a provisional stent. A provisional stent should be placed for an acute IVL failure defined as:

- Residual stenosis ≥50% by visual estimate, or
- Un-resolved flow-limiting (≥Grade D) dissection, or
- Trans-lesional gradient >10 mm Hg is observed.

Procedural Imaging Requirements

An angiographic cine image will be obtained for each lesion treated including pre-procedure, post-IVL and end of procedure. All angiographic images must be submitted to the core lab for analysis. Intravascular imaging (including IVUS or OCT) is optional. If performed, images from the three timepoints (pre-procedure, post-IVL and end of procedure) should be submitted to the Study Sponsor for analysis.

7.8 Follow-Up

7.8.1 Discharge or Within 12-24 Hours Post-Procedure

The following assessments and procedures will be performed within **12-24 hours** post procedure or prior to hospital discharge, whichever occurs first:

- Follow up visit assessments including:
  - Physical examination
    - Vital signs
    - Height and weight
    - Target review of symptoms
  - Adverse event assessment

7.8.2 30-Day Follow-Up

The following evaluations will be performed at **30 days** (+/-7 days) post procedure:

- Follow-up visit assessments including:
  - Physical examination
    - Vital signs
    - Height and weight
    - Target review of symptoms
  - ABI (at rest or after exercise; keep consistent with screening)
  - Rutherford Category
  - Review of medications

- Adverse event assessment

Note: If the 30-Day Visit cannot be performed on-site, a remote follow-up visit is acceptable. If visit is conducted remotely, ABI is not required (will not incur a protocol deviation).

7.8.3 6-Month Follow-Up

The following evaluations will be performed at **6 months** (+/-30 days) post procedure:

- Follow-up visit assessments including:
  - Physical Examination
    - Vital signs
    - Height and weight
    - Target review of symptoms
  - ABI (at rest or after exercise; keep consistent with screening)
  - Rutherford Category
  - Review of medications
  - Adverse event assessment

Note: If the 6-Month Visit cannot be performed on-site, a remote follow-up visit is acceptable. If visit is conducted remotely, ABI is not required (will not incur a protocol deviation).

7.8.4 12-Month Follow-Up

The following evaluations will be scheduled for **12 months** (+/-30 days) post procedure:

- Follow-up visit assessments including:
  - Physical Examination
    - Vital signs
    - Height and weight
    - Target review of symptoms
  - ABI (at rest or after exercise; keep consistent with screening)
  - Rutherford Category
  - Review of medications
  - Duplex Ultrasound
  - Adverse event assessment

7.8.5 Prior to Target Limb Revascularization

The following evaluations will be completed prior to any target limb revascularization to assess symptoms and functional status prior to revascularization:

- Physical Examination
  - Vital signs
  - Height and weight
  - Target review of symptoms
- ABI (at rest or after exercise; keep consistent with screening)

- Rutherford Category
- Review of medications
- Angiographic lesion assessment (Angiographic images for revascularization procedures associated with the target limb must be submitted to the core lab.)

7.9 Subject Withdrawal

A study subject has the right to discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. A subject that has withdrawn from the study will be treated according to standard of medical care and will not be replaced.

7.9.1 When and How to Withdraw Subjects

Subjects may be withdrawn with the medical discretion of the physician, or they may voluntarily withdraw their consent at any time without impact to their medical treatment. When a subject is withdrawn, all data obtained prior to the time of withdrawal may be submitted to the Study Sponsor and be included in the study database, unless otherwise requested by the subject in writing.

In the event a subject is lost to follow-up or cannot be contacted for post-treatment assessments, at least three attempts (two phone calls and a certified letter) will be made to locate the study subject, and these efforts will be documented. If the subject cannot be located, the subject's lost to follow-up status will be documented in the EDC and they will be exited from the study.

Should the subject expire, an adverse event and study exit/withdrawal form should be completed. Physician assessment is required to determine if the cause of death was possibly or definitely related to the M^{5+} IVL System. If available, copies of the death certificate and/or an autopsy report should be included in the research records. The Investigator may need to provide written notification to the IRB/EC upon the death of the study subject, dependent on the IRB/EC policies.

8.0 BENEFITS AND RISKS

8.1 Benefits

There are no guaranteed benefits from participation in the study. The study will provide safety and performance data associated with M^{5+}Peripheral IVL System treatment of calcified iliac and femoropopliteal arteries. These clinical results may inform physicians in determining the optimal treatment strategy for this patient population.

8.2 Risks

For detailed information on the risks of the devices used in the study procedure, including a complete list of warnings, precautions and potential adverse events, please refer to the Instructions for Use (IFU) for the M^{5+}Peripheral IVL System. It is important to ensure that the IFU referred to represents the generation of the device used in the study procedure.

8.3 Mitigation of Risks

Only those patients meeting each inclusion and no exclusion criteria will be enrolled into this study. Investigators will be qualified by education, training and experience to assume responsibility for the proper conduct of the clinical investigation. Risks of observed or theoretical adverse events will be mitigated through the Instructions for Use, physician training, patient selection in the study protocol and close monitoring of protocol adherence.

All efforts will be made to minimize risks specifically by:

- Site selection
- Ensuring compliance to the protocol and IFU
- Study monitoring
- Safety processes – protocol adverse event reporting requirements, CEC and data safety monitoring committee oversight, and safety reporting to regulatory authorities including Vigilance reporting

9.0 DATA ANALYSIS PLAN

9.1 General Statistical Methods

Descriptive statistics will be provided in this study. Analyses will be conducted at pre-specified time points including 30 days, 6 and 12 months.

Categorical data will be summarized using frequency tables, presenting the subject counts and percentages. McNemar's chi-square may be used to assess within-subject changes in a bivariate response variable.

Continuous variables will be summarized by the mean, standard deviation, median, minimum and maximum. Within-subject changes will be analyzed parametrically using the Paired t-test if the differences are normally distributed, or non-parametrically using the Sign-Rank Test if the differences are not normally distributed.

Exact confidence intervals will be generated for estimates of proportions. Asymptotic confidence intervals will be generated for estimates of means. The p-values of all tests will be reported without any correction for the multiplicity of tests performed.

Statistical analyses will be performed using SAS System® Version 9.4. Analyses will be performed on all subjects enrolled in the study cohort.

9.2 Sample Size Determination

This study will enroll a minimum of 40 lesions in up to 40 subjects at up to 10 sites in Australia, New Zealand and the US with the aim of treating at least 20 target lesions with the 8.0 mm IVL catheter. A maximum of three target lesions may be treated per subject. The results from this study will provide estimates of the primary and secondary safety and performance endpoints. Two-sided 95% Confidence Intervals will be calculated for each endpoint.

As a confirmatory study, the sample size was justified using methods similar to those that would be used to justify a feasibility study. Sample sizes justifications in research and medical device development vary with four main methodological approaches: rules of thumb, conceptual models, numerical guidelines derived from empirical studies, and statistical formulas (J. Sim, Saunders, Waterfield, & Kingstone, 2018). For feasibility studies, the rule of thumb approach is most often applied, and sample sizes between 12 and 50 have been recommended (Browne, 1995; Hertzog, 2008; Julious, 2005; J. Sim & Lewis, 2012; Stallard, 2012). The sample size for the PAD+ study (n=40) is in keeping with these published recommendations and is therefore justified.

Assuming a primary performance point estimate of 65% for Procedural Success (derived from the PAD III study of peripheral IVL using the M^5 catheter) (Gray, 2020), a sample size of 40 lesions would result in a 2-sided 95% CI of [48.3,79.4]. The lower bound of this interval is similar

to the PTA (control) arm of PAD III study (50.4%) (Gray, 2020), which is sufficient given the aims of the research.

These data provide reasonable evidence of safety and performance.

9.3 Populations for Analysis

Intent-To-Treat Cohort (ITT): All subjects who are enrolled in the study and where delivery of the IVL treatment is attempted are included in the ITT Cohort.

The primary analysis population will be the Intent-to-Treat cohort.

9.4 Handling of Dropouts or Missing Data

No imputation of or adjustments for missing data will be performed for the primary analyses. All available data will be presented. For time to event analyses, subjects will be censored at their last known follow-up.

10.0 SAFETY EVENTS

Standard definitions and reporting requirements for reportable adverse events for the study are provided below.

Note: For any of the Adverse Event Definitions listed below, diagnosis should be reported versus individual symptoms leading to diagnosis.

10.1 Adverse Event Definitions

10.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the study medical device.

Note: This definition includes events related to the investigational medical device.

Note: This definition includes events related to the procedures involved.

10.1.2 Serious Adverse Event (SAE)

An adverse event that

a) led to death

b) led to a serious deterioration in the health of a subject that either resulted in

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function, or

3) in-patient or prolonged hospitalization, or

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

Planned hospitalization for a pre-existing condition, or a procedure required by the study protocol without serious deterioration in health, is not considered a serious adverse event.

10.1.3 Adverse Device Effect (ADE)

An adverse device effect is defined as any untoward adverse event related to the use of an investigational or study medical device.

Note: This definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of an investigational medical device.

Note: This definition includes any event resulting from insufficiencies or inadequacies in the Instructions for Use, deployment of the device or any event that is a result of user error or intentional abnormal use of an investigational medical device.

10.1.4 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

10.1.5 Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect is any serious adverse effect on health or safety, 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 protocol or application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. 21 CFR 812.3(s)

10.1.6 Unanticipated Serious Adverse Device Effect (USADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the clinical investigations or Instructions for Use.

To further clarify, an Anticipated SADE (ASADE) is considered an effect, which by its nature, incidence, severity or outcome has been previously identified in the clinical investigations and Instructions for Use.

10.2 Adverse Event Device and Procedure Relatedness

Based on clinical judgment, the Investigator must provide a determination of device and procedure relationship for adverse events according to the following categories:

- Causal Relationship (Definite) – The adverse event is clearly related to the study device: the event has a temporal relationship to the study device, follows a known pattern of response, or is otherwise logically related to the study device, and no alternative cause is present.
- Probable – The adverse event is likely related to the study device: the event has a temporal relationship to the study device, follows a known or suspected pattern of response, or is otherwise logically related to the study device, but an alternative cause may be present.
- Possible – The adverse event is unlikely related to the study device: the event does not follow a clear temporal relationship to the study device or does not follow a known pattern of response, or is otherwise possibly to be due to the subject's clinical state or other modes of therapy.

  In some cases, the adverse event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. Maximum effort will be made to define and categorize the event and avoid these situations. If relatedness remains uncertain, then classify the event as "possible".
- Unlikely – The adverse event can be reasonably explained by another cause and/or the relationship with the use of the device seems not relevant, but additional information may be obtained.

- Not Related – The adverse event is clearly not related to the study device: the event has no temporal or other relationship to the administration of the investigational device follows no known or suspected pattern of response, and an alternative cause is present.

10.3 Device Deficiencies

10.3.1 Definitions

Device Deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (includes malfunctions, use errors, and inadequate labeling).

Note: Device deficiencies include malfunctions, use errors, and inadequate labeling.

Device Malfunction is a failure of the study medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or study protocol.

10.3.2 Reporting

All device deficiencies and malfunctions will be documented on the case report form and reported to the Study Sponsor within 48 hours after the designated study site personnel first learns of the event, and reported to the IRB/EC (if required) within the IRB/EC required timeframe.

If a deficiency or malfunction meets the definition of a product complaint (any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, or performance of a device after it is released for distribution), a Shockwave Medical Complaint Form will be completed by a Shockwave representative and entered into the company's complaint system. The Shockwave Medical Quality representative is responsible for assessing the need for and submitting any Vigilance and/or Medical Device Reporting (MDR) reports, if required.

10.4 Serious and Non-serious Adverse Event Reporting Requirements

10.4.1 AE Reporting Requirements

All AE information will be collected from enrollment through 12 months follow-up.

AEs should be reported in the subject's medical records as applicable and on the Adverse Event Case Report Form (AE CRF). Data reported should include date of onset, treatment, resolution, and an assessment of both seriousness and relationship to the study device and procedure. AEs will be followed until the event has resolved (in the case of permanent impairment, the event will be followed until it stabilizes and the overall clinical outcome has been ascertained).

Any AEs that meet IRB/EC reporting requirements must be reported per the institution's policy.

10.4.2 SAE Reporting Requirements

Any AE meeting any of the criteria for an SAE occurring at any time during the study (enrollment through 12 months) must be reported to the Study Sponsor within 48 hours after the designated study site personnel first learns of the event. The SAE must also be reported to the IRB/EC per the institution's policy for reporting SAEs. SAEs should be reported in the subject's medical records as

applicable and on the Adverse Event Case Report Form (AE CRF). Data reported should include date of onset, treatment, resolution, and an assessment of both seriousness and relationship to the study device and procedure. SAEs will be followed until the event has resolved (in the case of permanent impairment, the event will be followed until it stabilizes and the overall clinical outcome has been ascertained).

It is the responsibility of the Investigator to inform their IRB/EC of serious adverse events as required by their IRB/EC policies. The Investigator should forward a copy of this report to the Study Sponsor and file in the site regulatory binder.

If the device is suspected to have caused or contributed to the SAE, a Shockwave Medical Complaint Form will be completed by a Shockwave representative and entered into the company's complaint system. The Shockwave Medical Quality representative is responsible for assessing the need for and submitting any Vigilance and/or Medical Device Reporting (MDR) reports, if required.

10.4.3 Non-serious ADE Reporting Requirements

All ADE information will be collected from enrollment through 12 months. ADEs will be recorded in the subject's medical records as applicable and on the Adverse Event Case Report Form (AE CRF). Each ADE must be evaluated to determine if the event meets the definition of serious adverse device effects. Data reported should include date of onset, treatment, resolution, and an assessment of both seriousness and relationship to the study device and procedure. ADEs will be followed until the event has resolved (in the case of permanent impairment, the event will be followed until it stabilizes and the overall clinical outcome has been ascertained). All ADEs must be reported to the Study Sponsor as soon as possible after the designated study site personnel first learns of the event.

10.4.4 SADE Reporting Requirements

All ADEs will be evaluated by the Study Sponsor or designee to determine if the ADE meets the definition of a SADE. All SADEs must be reported within 48 hours after the designated study site personnel first learns of the event. All SADEs should be reported to the IRB/EC in accordance with their requirements.

If the device is suspected to have caused or contributed to the SADE, a Shockwave Medical Complaint Form will be completed by a Shockwave representative and entered into the company's complaint system. The Shockwave Medical Quality representative is responsible for assessing the need for and submitting any Vigilance and/or Medical Device Reporting (MDR) reports, if required.

10.4.5 UADE/USADE Reporting Requirements

Investigators are required to submit a report of a USADE to the Study Sponsor as soon as possible, but not later than 48 hours after the Investigator first learns of the event and to the IRB/ECs within the required timeframe. Investigators are required to report a UADE to the reviewing IRB/EC and the Study Sponsor as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.

If the device is suspected to have caused or contributed to the UADE/USADE, a Shockwave Medical Complaint Form will be completed by a Shockwave representative and entered into the company's complaint system. The Shockwave Medical Quality representative is responsible for assessing the need for and submitting any Vigilance and/or Medical Device Reporting (MDR) reports, if required.

10.4.6 AE and Device Deficiency Reporting Time Frames

Table summarizes the time sensitive reporting requirements for serious and non-serious adverse events and device deficiencies. The Study Sponsor or designee is the contact person for these reporting requirements.

Table 3. Investigator Responsibilities for Submitting Serious and Non-Serious Adverse Events to the Study Sponsor

Type of Event	Process
Device deficiencies (including malfunctions)	Submit within 48 hours after the designated study site personnel first learns of the event and to the IRB/EC (if required) within the IRB/EC required timeframe.
Serious adverse events (SAE, SADE)	Submit within 48 hours after the designated study site personnel first learns of the event and to the IRB/EC within the IRB/EC required timeframe.
Unanticipated adverse device effect (UADE, USADE)	Submit immediately to the Study Sponsor after the designated study site personnel first learns of the event and to the IRB/EC within the IRB/EC required timeframe.
Non-serious adverse events (AE, ADE)	Submit to the Study Sponsor as soon as possible after study personnel has become aware of the event, and to the IRB/EC (if required) within the IRB/EC required timeframe.

11.0 INVESTIGATOR RESPONSIBILITIES

The role of the Principal Investigator is to implement and manage the conduct of the clinical study at their site, as well as ensure data integrity and the rights, safety and well-being of the participating subjects.

11.1 IRB/EC Approval

The Investigator must obtain IRB/EC approval to conduct the study prior to screening any potential subjects and comply with annual continuing approval requirements. All correspondence with the IRB/EC should be maintained in the site's study files.

11.2 Informed Consent

The Investigator is responsible for ensuring that all applicable local, national, Declaration of Helsinki, and ISO 14155:2011 requirements for all devices in the study are met when completing the informed consent process. It is the responsibility of the Investigator to ensure written informed consent from each subject, or the legally authorized representative of the subject, is obtained prior to the initiation of any study-related procedures. The Investigator must comply with the requirements specified in protocol **Section 7.3**.

11.3 Protocol Compliance and Delegation of Authority

The Investigator shall conduct the clinical study in compliance with this study protocol and ensure that the study is appropriately staffed with qualified study personnel throughout the duration of the study. In addition, the facilities where the study is being conducted must be maintained to allow for proper study conduct. Changes to either study staff or facilities must be documented. The Investigator must maintain a Delegation of Authority Form of appropriately qualified persons to whom the Investigator has delegated significant study related duties.

11.4 Medical Care of Subjects

The Investigator shall:

- Provide adequate medical care to a subject during and after a subject's participation in the clinical study in the case of adverse events, as described in the informed consent,
- Inform the subject of the nature and possible cause of any adverse events experienced,
- Inform the subject of any new significant findings occurring during the clinical study, including the need for additional medical care that may be required,
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment,
- Ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical study,
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical study, and

- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from the clinical study while fully respecting the subject's rights.

11.5 Safety Reporting

The Investigator must comply with the safety reporting requirements specified in protocol **Section 10.0.**

11.6 Protocol Amendment(s)

The Investigator or clinical site staff will not make any modifications to this protocol or the Informed Consent form without prior written approval from the Study Sponsor. Study Sponsor and Investigator will agree to all amendments made to the protocol or the Informed Consent form. If protocol changes affect the scientific soundness of the clinical investigation, or affect the health, welfare, safety and rights of patients, Investigator and/or Study Sponsor will obtain written approval by the Investigator's IRB/EC, before implementing changes. All amendments must then be submitted to the IRB/local EC, as appropriate for approval.

11.7 Records Retention

All study records and documentation must be maintained by the Investigator and are subject to inspection and copying and must be retained for a period of two (2) years after the study is completed or terminated. The Study Sponsor must be contacted if the Investigator plans to leave the study site. An Investigator may withdraw responsibility to maintain records for the time required by the study protocol by transferring custody to another qualified person willing to accept responsibility for him/her.

12.0 STUDY SPONSOR RESPONSIBILITIES

As the Study Sponsor, Shockwave Medical is responsible for the overall conduct and quality of the study. Shockwave Medical will ensure that qualified monitors and designated personnel are monitoring the study according to the pre-determined monitoring plan and that the Informed Consent process is followed per the study site's requirements. The Study Sponsor is responsible for the classification and reporting of adverse events and ongoing safety evaluation of the clinical study.

12.1 Selection and Training of Study Sites

Investigators will be qualified by education, training and experience to assume responsibility for the proper conduct of the clinical investigation. Investigators must disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical investigation or interpretation of results.

Shockwave Medical and/or its designees are responsible for the training of appropriate clinical site personnel, including the Principal Investigator, Sub-Investigator(s), and Research Coordinator(s). Initial protocol and device training will be conducted by Shockwave Medical or its designees and will be ongoing as required.

A Training Record must be signed and dated by both Shockwave Medical and/or its designee conducting the training, and each member of the research team that attended the training session before any study activity is performed. A copy of the signed training records must be submitted to Shockwave Medical or its designee and the original signed training record(s) should be filed in the site's study Regulatory Binder.

12.2 Monitoring

12.2.1 Monitoring Methods

Monitoring functions will be conducted by Shockwave Medical and/or its designated Contract Research Organization (CRO). Specific monitoring requirements are detailed in the study-specific Monitoring Plan maintained in the Shockwave Medical and/or the CRO clinical study project files.

All monitoring activities shall be documented in a written report. Corrective action will be taken to resolve any issues of noncompliance. If Shockwave Medical finds that an Investigator is not complying with the executed Investigator Agreement, the study protocol, the applicable laws and regulations, or the requirements of the reviewing IRB/EC, prompt action will be taken to secure compliance. Shockwave Medical will reserve the right to suspend or terminate the participation of the Investigator or the study site.

12.2.2 Monitoring Visits

Scheduled monitoring visits to the clinical study site may occur at the following times: prior to the start of the study, interim visits throughout the clinical study as required per the monitoring plan, and upon completion of the clinical study. Sites that enroll rapidly may be visited more frequently at Shockwave Medical's discretion. A final Close-Out Visit will be conducted upon completion of the entire clinical study or at the time a site is terminated. Restrictions to on-site

monitoring visits may require that alternative monitoring strategies be implemented including use of remote monitoring or risk-based approaches.

12.3 Study Deviations

A study deviation is defined as an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the study protocol, applicable laws or regulations, or the Investigator Agreement. The Investigator must document and notify Shockwave Medical of any deviation from the study protocol as soon as possible. Requests for deviations, and reports of deviations, if the deviation affects the subject's rights, safety and well-being, or the scientific integrity of the clinical investigation will be reported to the IRB/EC, as required by their procedures.

Major deviations include those that involve the primary endpoint, the informed consent process and the inclusion/exclusion criteria of the study, or any deviation that involves or leads to a serious adverse event in a study subject.

Under certain circumstances, deviations from the study protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Study Sponsor and the IRB/EC. Such deviations shall be documented in writing and reported to the Study Sponsor and the IRB/EC as soon as possible, and no later than 5 working days.

Subject specific deviations will be reported on the Protocol Deviation case report form. Investigators will also adhere to procedures for reporting study deviations to their IRB/EC in accordance with their requirements. Deviations from clinical protocol will be reviewed and evaluated by Shockwave Medical on an ongoing basis and, as necessary, appropriate corrective actions put into place.

12.4 Device Accountability

The Study Sponsor will only provide investigational devices to the site once evidence of required IRB/EC approval has been provided to the Study Sponsor or designee.

The Investigator must keep complete, current and accurate records of the receipt, use, or disposition of investigational devices.

12.5 Study/Site Suspension or Early Termination

The Study Sponsor may suspend or prematurely terminate the study at either an individual site or the entire clinical study for significant and documented reasons. A Principal Investigator, IRB/EC, or regulatory authority may suspend or prematurely terminate participation in a clinical study at the sites for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the clinical study, or when so instructed by the IRB/EC or regulatory authorities, the Study Sponsor shall suspend the clinical study while the risk is assessed. The Study Sponsor shall terminate the clinical study if an unacceptable risk is confirmed.

Shockwave Medical shall consider terminating or suspending the participation of a particular study site or Investigator in the clinical study if monitoring or auditing identifies serious or

repeated deviations on the part of an Investigator. If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The Principal Investigator and Study Sponsor shall keep each other informed of any communication received from the IRB/EC or any regulatory authority.

If, for any reason, Shockwave Medical suspends or prematurely terminates the study at an individual site, the Study Sponsor shall inform the IRB/EC. If the suspension or premature termination was in the interest of safety, the Study Sponsor shall inform all other Principal Investigators.

If suspension or premature termination occurs, Shockwave Medical will remain responsible for providing resources to fulfill the obligations from the study protocol and existing agreements for follow up of the subjects enrolled in the clinical study, and the Principal Investigator or authorized designee shall promptly inform the enrolled subjects at his/her site, if appropriate.

Routine closeout activities shall be conducted to ensure that the Principal Investigator's records are complete, all documents needed for the Study Sponsor's files are retrieved, remaining clinical study materials are disposed of, previously identified issues have been resolved and all parties are notified.

Resumption of a Study after Temporary Suspension:

When the Study Sponsor completes an analysis of the reason(s) for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the Study Sponsor shall inform the Principal Investigators and the IRB/EC, and provide them with the relevant data supporting this decision. Concurrence shall be obtained from the IRB/EC before the clinical study resumes. If subjects have been informed of the suspension, the Principal Investigator or authorized designee shall inform them of the reasons for resumption.

12.6 Study Completion

The study is considered completed after all subjects have undergone all of their protocol required follow-up visits, data entry for all eCRFs has been completed, all queries have been resolved, all action items have been closed, and all site payments have been made. All unused study materials and study devices will be collected and returned to Shockwave Medical or appropriately discarded as per instruction. After study closure, a final study report will be completed, even if the clinical study was terminated prematurely.

12.7 Audits / Inspections

Shockwave Medical, regulatory agencies and IRBs/ECs may conduct audits or inspections at the study sites during the course of or after completion of the study. Access to all study records, including source documents, for inspection and duplication may be requested.

12.8 Publication Policies

The Study Sponsor and the study investigators are committed to timely and complete dissemination of the study results. Publications based on the results of the study will follow the process outlined in the Investigator Agreement. At the conclusion of the study, a multi-center manuscript will be prepared for publication in a reputable peer-reviewed scientific journal. The principal results will also be presented at a scientific congress.

The publication of the results from any single site experience within the study is not allowed until the preparation and publication of the multi-center results has occurred. Exceptions to this rule require the prior approval of Shockwave Medical.

After publication of the multi-center manuscript, a single site may publish the results of its subjects after first complying with the requirements in the Investigator Agreement. Any proposed publications must be submitted to Shockwave Medical for review and comment at least forty-five (45) days in advance of submitting such proposed publications to a publisher or other third party. If no response is received from Shockwave Medical within thirty (30) days of the date submitted, the Investigator may proceed with publication as long as all work and research on the clinical study has been completed.

This study is registered with www.clinicaltrials.gov and anzctr.org.au.

12.9 Data Management

Shockwave Medical and Data Management designees will oversee and/or perform all data management functions. Data management functions include database development, system maintenance, user training, data queries, and report generation. The Principal Investigator and/or study staff are responsible for the accuracy and completeness of all study data recorded. The Principal Investigator is responsible for confirming the integrity of the data and for full, transparent public reporting of the results. Aspects with respect to the management and storage of data will also be outlined in the Patient Informed Consent Form for site specific factors.

Shockwave Medical intends to utilize the data obtained from the study for commercial uses including publication and / or presentation of results at congresses, regulatory agency submissions, continued product development activities and marketing of their vascular products. All data when used in these activities will be in a de-identified format. Data obtained during this study will not be utilized in a database without first gaining the consent of participants.

12.9.1 Case Report Forms

All required data for this study will be collected via cloud-based electronic data capture (EDC) system and entered in electronic Case Report Forms (eCRFs).

All data collected during the study will be de-identified. For this purpose, a unique study identifier will be assigned to each study subject. All information recorded on the electronic Case Report form (eCRF) about the subject will be recorded including the study identifier. The database will contain only the study identifier to identify the subject. The code with subject

name and study number will be maintained by the Principal Investigator in a secured location. Subjects names will not be released to Shockwave Medical at any stage of the study.

12.9.2 Transmission of Data

For electronic CRFs:

Required data will be recorded on the appropriate electronic Case Report Forms at the time of or as soon as possible after the subject visit. The eCRF and any requested supporting source documents (including medical imaging files) must be sent to Shockwave Medical and/or retrieved from the Investigator during monitoring visits. Where possible, data sent to Shockwave Medical will be done so utilizing a password secured cloud-based system.

12.9.3 Data Queries

Any data discrepancies identified during data review or a monitoring visit will be queried by Shockwave Medical or its designee and must be resolved by the investigational site staff and Investigator in a timely manner.

Data audits may be performed for quality assurance of data handling. Any discrepancies will be queried by Shockwave Medical or its designee and must be resolved by the investigational site staff and Investigator in a timely manner, particularly during those times data is being prepared for CEC safety reviews and reports required by the regulatory authorities.

12.9.4 Study Sponsor Data Retention

Shockwave Medical will retain all study data received for a period of two (2) years after the investigation is completed or terminated, or two (2) years after the records are no longer required to support the application to market the device (whichever date is later), or longer if required by applicable local regulations. The data will be retained in a secure, password protected database and stored in the United States of America.

13.0 STUDY COMMITTEES

13.1 Clinical Events Committee (CEC)

To meet the ethical responsibilities and standards for research subjects, an independent Clinical Events Committee shall serve as forum for adjudication of certain pre-specified clinical event types described in the CEC charter. In order to enhance objectivity and reduce the potential for bias, the CEC shall be independent of the Study Sponsor as well as the study sites / Investigators.

The CEC is made up of clinicians with pertinent expertise who are not participants in the study and who do not have any other real or potential conflicts of interest. The CEC is charged with the development of specific criteria used for the categorization of adverse events and clinical endpoints in the study. Criteria will be established for selected complications and clinical events.

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 an event. The methodology for performing these responsibilities shall be developed and outlined in the CEC Charter. Operational provisions shall be established to minimize potential bias (i.e., CEC members shall be blinded to the clinical site to the extent possible during adverse event review and adjudication). The methodology for performing these responsibilities shall be developed and outlined in the CEC Charter.

14.0 ETHICAL and REGULATORY CONSIDERATIONS

14.1 Role of Shockwave Medical

As the Study Sponsor of this clinical study, Shockwave Medical has the overall responsibility for conduct of the study, including assurance that the study will be conducted according to ICH Good Clinical Practices (GCP), 21 CFR 812, 820, 50, 54, and 56, Declaration of Helsinki, applicable IRB/EC requirements, as well as any ISO 14155 and/or national requirements. In this study, Shockwave Medical will have certain direct responsibilities and may delegate other responsibilities to qualified consultants and/or contract research organizations. The specific federal regulations, international standards, and/or guidelines required to be followed should be outlined within the protocol.

This protocol and any amendments will be submitted to each site's IRB/EC for formal approval of the study. All subjects considered for this study will be provided a consent form describing this study and providing sufficient information for them to make an informed decision about their participation.

14.2 Subject Confidentiality

Subject confidentiality will be maintained throughout the clinical study. A unique subject identification code will be assigned and used to allow identification of all data reported for each subject.

Study data may be made available to third parties, e.g., in the case of an audit, provided the data are treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event that study data are published.

15.0 DEFINITIONS and ABBREVIATIONS

15.1 Study Definitions

Access Site Hemorrhage: Bleeding from the access site which requires transfusion, hospitalization (either admission or extended stay), or further treatment for management. Hemorrhage, without frank bleeding, needing ≥1 unit RBCs will be considered a serious adverse event.

Access Site Infection: Culture-proven wound infection or presumptive treatment with antibiotics for clinically diagnosed wound infection.

Acute Renal Failure: Acute post-operative renal insufficiency resulting in one or more of the following: (a) increase of >1.0 mg/dl in serum creatinine from most recent prior measured level, and current measured absolute value is >2.0 mg/dl; (b) a new requirement for dialysis.

Adverse Device Effect (ADE): An adverse event related to the use of the medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. This definition includes any event that is a result of a user error.

Note: This definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

Note: This definition includes any event resulting from insufficiencies or inadequacies in the Instructions for Use, deployment of the device or any event that is a result of user error or intentional abnormal use of the investigational medical device.

Adverse Event (AE): An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational device/procedure.

Air Embolism: An inadvertent introduction of air or gas to the vasculature that requires medical treatment.

Allergic Reaction: An allergic reaction characterized by rash, nausea, vomiting, upper respiratory congestion, urticaria, shortness-of-breath, vasovagal reaction, or general cardiovascular collapse (anaphylaxis).

Amputation (major): Any requirement for amputation above the ankle or higher.

Amputation (minor): Any requirement for amputation below the ankle.

Amputation, Unplanned: An amputation associated with the target limb that occurs between the index procedure and 30 days that was not previously planned as part of the overall treatment strategy.

Anemia: Decrease from baseline in red blood cells, hemoglobin, or total blood volume that is associated with hemodynamic changes or requires transfusion, or a drop in hematocrit to below 30%. Any documented anemic event requiring ≥2 units PRBCs will be considered an SAE.

Angina: A tight or heavy feeling in the chest, discomfort which spreads from the chest to the arm, back, neck, jaw, or stomach, numbness or tingling in the shoulders, arms or wrists, shortness of breath, and nausea relieved by rest or nitroglycerin.

Angina, unstable: Chest pain that increases in frequency, intensity, or duration, which occurs at rest, or which is new in onset. Unstable angina is a syndrome that is intermediate between stable angina and myocardial infarction: it is characterized by an accelerating or "crescendo" pattern of chest pain that lasts longer than stable angina, occurs at rest or with less exertion than stable angina, or is less responsive to medication. Unstable angina and myocardial infarction are considered acute coronary syndromes.

Ankle / Brachial Index (ABI): The ratio of systolic blood pressure measured at the ankle to systolic blood pressure measured at the brachial artery.

Arterial Occlusion / Thrombosis at Puncture Site: Angiographic or ultrasonographic evidence of occlusion at the puncture site limiting antegrade flow to the distal limb.

Arterial Perforation/Rupture/Puncture of an Arterial Wall: Classified as follows:
Angiographic perforation: Perforation detected by the clinical site at any point during the procedure.

Clinical perforation: Perforation requiring additional treatment (including efforts to seal the perforation), or resulting in significant extravasation of blood from the site, abrupt closure, limb ischemia or death.

Arterial Pseudoaneurysm: Disruption of arterial wall confirmed by imaging study and requiring intervention.

Arteriovenous Fistula (AVF): An abnormal passage or communication between an artery and a vein which may be due to the percutaneous introduction of ancillary devices (e.g., needles, catheters, guide wires) confirmed by imaging studies.

Atypical Chest Pain: Located under the sternum, left chest, abdomen, back, or arm and is fleeting or sharp. It is unrelated to exercise, not relieved by rest or the administration of nitroglycerin.

Bacteremia: Presence of viable bacteria in the circulating blood. May be associated with clinical signs/symptoms such as fever. Must be confirmed by having one positive blood culture and no subsequent negative cultures.

Bleeding Complication (Major): Bleeding resulting in ≥3 g/dl decrease in hemoglobin (if hemoglobin level not available, a decrease in hematocrit of ≥ 10%), or necessitating transfusion of >1 unit of PRBC's /whole blood, or necessitates surgery/endoscopic intervention.

Access site: Bleeding from the arteriotomy site which requires transfusion, hospitalization (either admission or extended stay), or further treatment for management.

Calcification Classification (study eligibility): Calcification must be: 1) on parallel sides of the vessel and 2) extending >50% the length of the lesion if lesion is ≥50mm in length; or extending for minimum of 20mm if lesion is <50mm in length.

Calcification Classification (PARC): Calcification will be assessed by the angiographic core lab according to the Peripheral Academic Research Consortium (PARC) definition (Patel et al., 2015).

PARC Degree of Lesion Calcification

Focal	Degree of lesion calcification
Mild	<180° and greater than one-half of the total lesion length
Moderate	≥180° (both sides of vessel at same location) and less than one-half of the total lesion length
Severe	>180° (both sides of the vessel at the same location) and greater than one-half of the total lesion length

CAPA: Corrective and Preventative Action.

Cardiac Arrhythmia: Electrical disruption of the heart rhythm requiring specific medication, defibrillation, or pacemaker insertion to address condition.

Cardiogenic Shock: Subject presents with SBP <80 mm Hg for more than 30 minutes, unresponsive to fluids, or requiring intravenous vasopressor agent or an intra-aortic balloon pump (IABP).

Cardiovascular Death: All cardiovascular cause mortality.

Cerebral Vascular Accident (CVA): See Stroke.

Closure, Abrupt: Occurrence of new (during the index procedure), persistent slow, reduced, or loss of flow within the target vessel that requires intervention other than the index or adjunct treatment. Abrupt closure may also be referred to as acute occlusion if there is a total loss of flow.

Closure, Subacute: Target lesion site occlusion that occurs after the index procedure is completed (e.g., the subject has left the treatment area) and within 30 days of procedure.

Congestive Heart Failure: Documentation of one of the following: a) paroxysmal nocturnal dyspnea (PND), b) dyspnea on exertion (DOE) due to heart failure, or c) elevated pulmonary capillary wedge pressure (PCWP) with associated shortness of breath (SOB) or x-ray consistent with congestion. May be related to fluid overload in the presence of underlying cardiovascular disease.

Contrast-Induced Nephropathy: Associated with contrast agent resulting in >25% increase in serum creatinine or an absolute value of >0.5 mg/dl.

Contrast Media Reaction: An allergic reaction, immediate or delayed, associated with the intravascular administration of contrast media that results in symptoms (e.g., itching, hives) or physiologic changes requiring treatment (e.g., anaphylactic reaction) or death.

Critical Limb Ischemia: Clinical manifestation of peripheral arterial disease characterized by Rutherford Clinical Scale Category of 2-6. (For the purposes of this study, only subjects with Rutherford Clinical Scale Category of 2, 3, 4, and 5 are eligible for enrollment).

Death: (divided into 2 categories)

Cardiac death is death due to any of the following:

1. Acute myocardial infarction
2. Cardiac perforation/pericardial tamponade
3. Arrhythmia or conduction abnormality
4. Stroke within 30 days of the procedure or stroke suspected of being related to the procedure
5. Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery
6. Any death for which a cardiac cause cannot be excluded

Non-cardiac death is a death not due to cardiac causes (as defined immediately above).

De novo: A segment of artery that has not previously been treated with angioplasty or stenting.

Deep Vein Thrombosis (DVT): Thrombosis of a deep vein, as confirmed by imaging study or direct visualization.

Device Deficiency: is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (includes malfunctions, use errors, and inadequate labeling).

Device Malfunction: A malfunction of a device is an unexpected change to the device that is contradictory to the Instructions for Use and may or may not affect device performance.

Dissection: Disruption of an arterial wall resulting in separation of the intimal layer. May or may not be flow limiting.

Dissection Classifications (National Heart, Lung and Blood Institute – NHLBI)

Type A: Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.

Type B: Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles.

Type C: Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material.

Type D: Spiral shaped filling defect without delayed run-off of the contrast material in the antegrade flow.

Type E: Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen.

Type F: Filling defect accompanied by total coronary occlusion.

Disseminated Intravascular Coagulation (DIC): A syndrome arising as a complication of many different serious and life-threatening illnesses. In its acute form it is a hemorrhagic disorder, characterized by multiple ecchymoses, mucosal bleeding, and depletion of platelets and clotting factors. Chronic DIC is more subtle and involves thromboembolism accompanied by evidence of activation of the coagulation system.

Dizziness: Imprecise term commonly used to describe various symptoms such as faintness, giddiness, imbalance, lightheadedness, unsteadiness, or vertigo.

Drug Reactions: An unwanted or harmful side effect experienced following the administration of a drug or combination of drugs and is suspected to be related to the drug.

Embolization, Distal: Any distal emboli confirmed by imaging considered to be related to the target lesion(s).

Embolization, Symptomatic: Clinical signs or symptoms of distal emboli detected in the treated limb distal to the treated lesion after the index procedure **or** noted angiographically and requiring mechanical or pharmacologic means to improve flow. This includes new abrupt occlusions or filling defects.

Femoropopliteal DVT: defined as DVT involvement limited to the superficial femoral or popliteal veins, with or without distal (e.g., toward foot) DVT involvement, based on duplex ultrasound exam.

Fever: A temperature 38°C (>101.4° F) not related to a culture positive infection.

General Discomfort: Physical or psychosocial signs or symptoms commonly associated with hospitalization that are investigated and determined to require minor (i.e., aspirin, non-narcotic medication) or no treatment.

Hematoma: Collection of blood (or its degradation products) which exceeds 5 cm in diameter, requires treatment, or prolongs hospitalization.

Hemorrhage: Any bleeding which results in a drop in hematocrit from pre-procedure level which is associated with hemodynamic compromise or which results in a hematocrit of ≤30%, or blood loss that requires transfusion.

Hypertension: Systolic BP >140 mmHg, or diastolic >90 mmHg requiring specific medical therapy.

Iliofemoral DVT: Defined as DVT involvement of the common or external iliac veins or the common femoral vein, with or without distal (e.g., toward foot) DVT involvement, based on duplex ultrasound exam.

Infection, access site: Infection at the vascular access site, documented by lab culture or clinical evidence requiring medical treatment (irrigation, debridement, antibiotics, etc.) to resolve.

Infection, sepsis: Culture-proven infections or presumptive treatment with antibiotics for clinically diagnosed infection.

Infection, systemic: Systemic infection documented by positive lab culture or clinical evidence, requiring medical treatment to treat and resolve.

Intracranial Hemorrhage: Includes all bleeding within the cranium either subarachnoid, intra-parenchymal, or intracerebral.

Intravascular Lithotripsy (IVL), formerly known as Intravascular Lithoplasty: Shockwave Medical's proprietary balloon angioplasty catheter including lithotripsy technology that creates pulsatile mechanical energy for disrupting calcified vascular plaque.

Limb Ischemia: Deficient supply of oxygenated blood to the tissues in the limbs that is due to obstruction of the inflow of arterial blood characterized by pain and/or discoloration of the limb.

Lithotripsy: A medical procedure for disrupting calculus in the body.

Luminal Patency: Post-procedure residual stenosis <50% as determined by investigator visual assessment or quantitative analysis of the end of procedure angiogram.

Major Adverse Event (MAE): For the purposes of this study, the definition of Major Adverse Event(s) includes:

- Need for emergency surgical revascularization of target limb
- Unplanned target limb major amputation (above the ankle)
- Symptomatic thrombus or distal emboli that require surgical, mechanical or pharmacologic means to improve flow and extend hospitalization
- Perforations that require an intervention, including bail-out stenting

Myocardial Infarction (MI): Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

Perforation: Puncture of an arterial wall.

Pneumonia: Diagnosed by one of the following: Positive cultures of sputum, blood, pleural fluid, emphysema fluid, transtracheal fluid or transthoracic fluid; consistent with the diagnosis and clinical findings of pneumonia. Should include chest x-ray diagnostic of pulmonary infiltrates.

Procedural Success: Procedural success is defined as final residual stenosis ≤30% without flow-limiting dissection (≥ grade D) by angiographic core lab.

Pseudoaneurysm: Disruption of the arterial wall characterized by an out-pouching or pocket with swirling, flowing blood outside of the confines of the arterial lumen.

Recurrent Occlusion: Occlusion (i.e., total obstruction of vessel lumen) after a successful canalization.

Recurrent Thrombosis: Thrombosis (i.e., sub-total obstruction of vessel lumen) following successful treatment.

Renal failure (Acute): Acute post-operative renal insufficiency resulting in one or more of the following: (a) increase of >1.0 mg/dl in serum creatinine from most recent prior measured level, and current measured absolute value is >2.0 mg/dl; (b) a new requirement for dialysis.

Renal Insufficiency: An increase in serum creatinine of ≥1.0 mg/dl over previous value requiring medical treatment but which does not require dialysis to resolve.

Respiratory Failure: New onset of respiratory insufficiency that requires placement of endotracheal tube and/or pneumothorax with or without chest tube.

Respiratory Insufficiency: Deterioration of subject's respiratory efforts that require supportive or medical treatment.

Retroperitoneal bleed: Bleeding into the back of the abdomen from a vascular access or puncture site.

Restenosis: Reoccurrence of narrowing or blockage of target lesion.

Rutherford Clinical Category Scale: Clinical scale identifying three grades of claudication and three grades of critical limb ischemia ranging from rest pain alone to minor and major tissue loss. (ACC/AHA PAD Practice Guidelines – Hirsch et al. 2005)

Grade	Category	Clinical Description
	0	Asymptomatic
I	1	Mild claudication
	2	Moderate claudication
	3	Severe claudication
II	4	Ischemic rest pain
	5	Minor tissue loss
III	6	Ulceration or gangrene

Septicemia: One positive blood culture AND clinical evidence for infection (e.g., fever, elevated WBC count, hypotension, need for increased inotropic support, end organ dysfunction, coagulopathy/ DIC [disseminated intravascular coagulation], need for increased ventilator support, etc.).

Serious Adverse Device Effect (SADE): A serious adverse device effect is defined as an adverse device effect that results in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken, intervention had not been made, or if circumstances had been less opportune.

Serious Adverse Event (SAE): A serious adverse event (SAE) is defined an adverse event that:

- led to death,
- led to a serious deterioration in the health of the subject, that either resulted in:
    - a life-threatening illness or injury, or
    - resulted in a permanent impairment of a body structure or a body function, or
    - required in-patient hospitalization or prolongation of existing hospitalization, or
    - resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function, or,
    - led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the investigational plan without serious deterioration in health, is not considered a serious adverse event.

Stroke: any neurological deficit lasting 24 hours or longer, or lasting less than 24 hours with a brain imaging study showing infarction consistent with deficit. May be further categorized as:

- Ischemic Stroke: neurologic deficit meeting the study definition for Stroke that is attributed to thromboembolic event.

- Hemorrhagic Stroke: neurologic deficit meeting the study definition for Stroke that is attributed to bleeding into brain tissue, epidural, subdural, or subarachnoid space; or a combination of these sites.

Target Lesion Revascularization, Clinically-driven (TLR):
A target lesion revascularization performed due to target lesion diameter stenosis ≥50% and either evidence of clinical or functional ischemia (e.g., recurrent/progressive life-limiting intermittent claudication, claudication unresponsive to medical therapy, CLI) or recurrence of the clinical syndrome for which the initial procedure was performed. Clinically driven target lesion revascularization occurs in the absence of protocol directed surveillance ultrasound or angiography.

Target Vessel Revascularization, Clinically-driven (TVR), non-TLR: A target vessel revascularization performed due to non-target lesion diameter stenosis ≥50% and either evidence of clinical or functional ischemia (e.g., recurrent/progressive life-limiting intermittent claudication, claudication unresponsive to medical therapy, CLI) or recurrence of the clinical syndrome for which the initial procedure was performed. Clinically driven target vessel revascularization occurs in the absence of protocol directed surveillance ultrasound or angiography.

Total Occlusion A 100% stenotic lesion as documented by angiographic absence of flow.

Thrombocytopenia: A persistent decrease in the number of blood platelets to subnormal levels.

Thrombus: Blood clot that obstructs a blood vessel.

Transient Ischemic Attack (TIA): Focal neurologic abnormalities of sudden onset and brief duration (i.e., lasting less than 24 hours and, if an imaging study is performed, shows no evidence of infarction).

Toe / Brachial Index (TBI): The ratio of systolic blood pressure measured at the toe to systolic blood pressure measured at the brachial artery.

Unanticipated Adverse Device Effect (UADE): 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 the device, if that adverse effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unanticipated Serious Adverse Device Effect (USADE): A serious adverse device effect that has not been expected to occur with the device or during the course of the study procedures and has not otherwise been identified as a possible risk in the clinical investigations.

Unstable Angina: Angina which increases in frequency, intensity, or duration, which occurs at rest, or which is new in onset. Unstable angina is a syndrome that is intermediate between stable angina and myocardial infarction: it is characterized by an accelerating or "crescendo" pattern of chest pain that

lasts longer than stable angina, occurs at rest or with less exertion than stable angina, or is less responsive to medication. Unstable angina and myocardial infarction are considered acute coronary syndromes.

Vascular Occlusion / Thrombosis at Puncture Site: Angiographic or ultrasonographic evidence of occlusion at the puncture site limiting flow to the limb.

Vasovagal Reaction: Reflex stimulation of the vagus nerve causing slowing of the heartbeat, decreased blood pressure, etc. and requires treatment consisting of any of the following: (a) >1 liter of IV fluids; (b) postural changes; (c) pacing intervention; or (d) administration of atropine.

15.2 List of Abbreviations

ABI	Ankle-brachial Index
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
CEC	Clinical Events Committee
CRF	Case Report Form
CRO	Contract Research Organization
DUS	Duplex Ultrasound
EDC	Electronic Data Capture
EC	Ethics Committee
FDA	Food and Drug Administration
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intent-to-Treat
IVL	Intravascular Lithotripsy
MAE	Major Adverse Event
OTW	Over the Wire
PAD	Peripheral Artery Disease
RC	Rutherford Category
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

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17.0 SUBJECT INFORMED CONSENT

The subject informed consent template will be provided as a separate attachment.

18.0 CASE REPORT FORMS

Draft case report forms will be provided as a separate attachment.

19.0 REVISION HISTORY

Revision	Release Date	DCO #	Reason(s) for Revision	Doc Owner
A	9/30/2020	21051	Initial release.	Clinical
B	10/7/2020	21069	Added longer catheter working length to the study rationale; revised angiographic inclusion criteria #8 to reflect vessel diameter for common iliac; added option for intravascular imaging to schedule of events and procedural discussion; administrative changes.	Clinical
C	10/19/2020	21128	Updated Index Procedure section with additional sizing recommendation and revised sequence chart based on current IFU; corrected visit label in Schedule of Events; added explanatory language in Data Management section to be in compliance with NZ National Ethical Standards; removed DSMB reference as not applicable, administrative changes.	Clinical

Revision	Release Date	DCO #	Reason(s) for Revision	Doc Owner
D	4/27/2021	21704	• Updated study objective to indicate that the study is being conducted in the US to evaluate continued safety and effectiveness in a postmarket setting with a cleared medical device. • Updated to include US centers following FDA clearance of the M5+ catheter. • Clarified use of devices allowed for treatment of non-target lesion(s). • Added additional explanatory text for sample size determination. • Clarified MDR reporting requirements pertaining to serious adverse events.	Clinical