Mini-S Feasibility Study

Prospective, Multi-center, Single-arm Feasibility Study of the Shockwave Medical Mini S Peripheral Intravascular Lithotripsy (IVL) System

Clinical Study Protocol Version D

21 July 2023

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Protocol Number: CP 65324

Protocol Date: 21 July 2023

Revision: D

Study Device: Shockwave Medical Mini S Peripheral Intravascular Lithotripsy (IVL) Catheter

Study Sponsor Name and Address: Shockwave Medical, Inc.
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Santa Clara, CA 95054
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1.0 INVESTIGATOR SIGNATURE PAGE

Study Title: Prospective, Multi-center, Single-arm Feasibility Study of the Shockwave Medical Mini S Peripheral Intravascular Lithotripsy (IVL) System

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5403 Betsy Ross Drive
Santa Clara, CA 95054
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 (ICH/GCP), ISO14155:2020, 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 Feasibility Study of the Shockwave Medical Mini S Peripheral Intravascular Lithotripsy (IVL) System (Mini S Feasibility Study)
Study Objective	To assess the safety and performance of the Shockwave Medical Mini S Peripheral IVL System for the treatment of heavily calcified, stenotic peripheral arteries.
Study Device(s)	Shockwave Medical Peripheral IVL System with Mini S IVL Catheter (Standard and Flex configurations)
Indications for Use	The Mini S IVL Catheter is intended for lithotripsy-enhanced catheter dilatation of lesions, including calcified lesions found in the peripheral vasculature, such as the iliac, femoral, ilio-femoral, popliteal, infra-popliteal, and renal arteries. The Mini S IVL Catheter is not for use in the coronary or cerebral vasculature.
Study Design	Prospective, multi-center, single-arm feasibility study
Enrollment	Up to 50 subjects with a minimum of 10 BTK lesions treated at up to 6 sites in Australia and New Zealand. A maximum of two (2) target lesions may be treated per subject.
Study Duration / Follow-Up Period	Subjects will be followed through discharge, 30 days, 6 and 12 months. Duplex Ultrasound (DUS) assessments required at 12 months. Total anticipated study duration approximately 26 months.
Subject Population	Subjects with moderate to severely calcified peripheral artery disease (PAD) with target lesion located in a native, *de novo* superficial femoral, popliteal or infrapopliteal artery.
Primary Safety Endpoint	**Major Adverse Events (MAE)** at 30 days defined as a composite of: o Cardiovascular death o Clinically-driven target lesion revascularization (CD-TLR) o Unplanned target limb major amputation (above the ankle)
Primary Performance Endpoint	**Technical Success** defined as *final* residual stenosis ≤50% without flow-limiting dissection (≥ Grade D) of the target lesion by angiographic core lab.

Secondary Endpoints	• **Serious angiographic complications** (defined as flow-limiting dissection (≥ grade D), perforation, distal embolization, or acute vessel closure as assessed by the angiographic core lab.
	• **IVL Technical Success (post-dil)** defined as *post-dilatation* residual stenosis ≤50% without flow-limiting dissection (≥ Grade D) of the target lesion by angiographic core lab (measured immediately following mandatory post-dilatation).
	• **IVL Device Success** defined as the ability to deliver, advance across the target lesion, pressurize, pulse, flush and retrieve the JAVELIN IVL Catheter.
	• **Technical success (final)** defined as *final* residual stenosis ≤30% without flow-limiting dissection (≥ Grade D) of the target lesion by angiographic core lab.
	• **Major Adverse Events (MAE)** at 6 and 12 months (as a composite and individual components)
	• **Primary Patency** at 12 months defined as:
	  ○ Above the knee lesions: freedom from ≥50% restenosis as determined by Duplex Ultrasound (DUS) and freedom from Clinically-Driven Target Lesion Revascularization (CD-TLR)
	  ○ Below the knee lesions: freedom from both total occlusion (100% diameter stenosis by DUS) in all of the target lesions in a flow pathway, as well as a CD-TLR
	Device performance endpoints will be reported for all Mini S IVL Catheters.

Study Inclusion Criteria	Subjects are required to meet all of the following inclusion criteria in order to be enrolled in the study. For lesion characteristics, each target lesion must meet eligibility. A maximum of two (2) target lesions may be treated per subject; target lesions may be in the same limb or in different limbs. **General Inclusion Criteria** 1. Age of subject is ≥ 18 years. 2. Subject is able and willing to comply with all assessments in the study. 3. Subject or subject's legal representative has been informed of the nature of the study, agrees to participate, and has signed the approved consent form.

	4. Estimated life expectancy > 1 year. 5. Rutherford Clinical Category 2, 3, 4 or 5 of the target limb(s). **Angiographic Inclusion Criteria** 6. One or two target lesion(s) located in a native de novo superficial femoral, popliteal or infrapopliteal artery (above the ankle joint), in one or both limbs. 7. Target lesion reference vessel diameter (RVD) between 2.0 mm and 7.0 mm by investigator visual estimate. 8. Target lesion stenosis ≥70% (for vessels below the knee defined as P3 to the ankle joint) or ≥90% (for vessels above the knee) by investigator visual estimate. 9. Target lesion length is ≤150 mm by investigator visual estimate. Target lesion can be all or part of the 150 mm treated zone. • Tandem lesions (lesions < 3 cm apart) are allowed if the total treated area covers the entire diseased segment. Total treated area is defined as the area treated by any device (pre-dilatation, IVL, post-dilatation, or destination therapy). Each tandem lesion/diseased segment is considered one target lesion. • If these segments are treated independently (i.e., no PTA treatment between two lesions) then this is considered two separate target lesions. 10. 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 (target limb). 2. History of endovascular or surgical procedure on the target limb within the last 30 days, or planned within 30 days of the index procedure, with the exception of toe amputation. Note: inflow treatment of non-target lesions is allowed providing successful treatment. 3. Subject in whom antiplatelet or anticoagulant therapy is contraindicated.

	4. Subject has known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-treated. 5. Subject has known allergy to urethane, nylon, or silicone. 6. Myocardial infarction within 60 days prior to enrollment. 7. History of stroke within 60 days prior to enrollment. 8. Subject has acute or chronic renal disease with eGFR <30 ml/min/1.73 m2 (using CKD-EPI formula), unless on renal replacement therapy. 9. Subject is pregnant or nursing. 10. Subject is participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint. 11. 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. 12. Covid-19 diagnosis within 30 days. 13. Planned use of cutting/scoring balloons, re-entry or atherectomy devices in target lesion(s) during the index procedure. 14. Planned major amputation of target limb. 15. Acute limb ischemia. 16. Occlusion of all the inframalleolar outflow arteries/vessels (i.e., desert foot). 17. Subject already enrolled into this study. **Angiographic Exclusion Criteria** 18. Failure to successfully treat clinically significant inflow lesions in the ipsilateral iliac, femoral, or popliteal arteries, defined as ≤30% residual stenosis with no serious angiographic complications (e.g. embolism). 19. Failure to successfully treat significant non-target infra-popliteal lesions, if treated prior to treatment of target lesion(s). Successful treatment is defined as obtaining ≤50% residual stenosis with no serious angiographic complications (e.g., embolism). 20. Target lesion includes in-stent restenosis.

	21. Evidence of aneurysm or thrombus in target vessel. 22. No calcium or mild calcium in the target lesion. 23. Target lesion within native or synthetic vessel grafts. 24. 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.

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3.0 INTRODUCTION

3.1 Background

3.1.1 Peripheral Arterial Disease

Peripheral arterial disease (PAD) is one of the most common indications of atherosclerotic disease and impacts more than 200 million people globally [1]. PAD is caused by the accumulation of plaque in the arteries that do not supply the brain or the heart. Although it can involve the renal arteries and/or the arteries of the neck or arms, PAD normally develops in the lower extremities. The reduced blood flow may lead to pain, tissue loss and eventual foot/leg amputation or death. Risk factors for PAD include advanced age, smoking, hypertension, diabetes and concomitant cardiovascular disease [1]. Calcified PAD is associated with coronary artery disease, diabetes and chronic kidney disease [2].

Early diagnosis and treatment of PAD reduces an individual's risk of cardio- or cerebrovascular disease morbidity and mortality [3]. Percutaneous endovascular therapies are being increasingly employed as the primary revascularization treatment for PAD, including calcified occlusions [4-6]. Endovascular therapies include percutaneous angioplasty (PTA), nitinol stents, directional and rotational atherectomy, laser atherectomy, drug-eluting stents (DES) and drug-coated balloons (DCB) [6].

Infrapopliteal atherosclerosis is a multilevel disease affecting below-the-knee (BTK) arteries and is often associated with critical limb ischemia (CLI). CLI represents the most severe form of PAD and is characterized by ischemic rest pain and/or nonhealing ulcers [7]. BTK lesions are often technically challenging to treat due to long length, small vessel diameter, poor outflow, and severe calcification [8]. Vessel wall calcification is more severe in BTK lesions compared to more proximal lesions, with medial calcification being most prevalent in the infrapopliteal segment. Due to the severity and unequal distribution of calcium in infrapopliteal lesions, vessel wall expansion can occur in a non-uniform manner increasing the risk for severe dissection with high pressure balloon dilatation [8]. Procedural success for infrapopliteal lesions has improved; however, recoil, dissections, and restenosis remain limitations of infrapopliteal endovascular procedures [9].

In sub-total occlusions with the narrowest crossing channels, microcatheters, with soft tips, tapered shapes, and variety of wire selections may be used to cross a lesion and allow for subsequent dilatation. Nevertheless, severe tortuosity and severe calcification remain barriers to microcatheter success, leading to excessively high rates of complications (typically either dissection and/or perforation) [10].

3.1.2 Intravascular Lithotripsy

Intravascular lithotripsy is a balloon-based calcium modification treatment modality that uses acoustic pressure waves to modify vessel wall calcium. Peripheral IVL is designed to improve vessel wall compliance to optimize acute gain while minimizing acute vessel injury. The safety and effectiveness of IVL has been reported in several clinical studies in moderate to severely

calcified PAD across multiple vessel beds [11-19], including the Disrupt PAD BTK study and the Disrupt PAD III Observational Study (OS), which evaluated peripheral IVL in BTK lesions.

The DISRUPT BTK study enrolled 20 patients with moderate to severely calcified infrapopliteal lesions with 30-day follow-up [14]. After treatment with IVL using the first generation M^5 catheter, all patients achieved a residual stenosis ⩽50%. There was only one type B dissection, and a total of two (2) stents were placed. These initial promising results supported the use of IVL to maximize lumen gain while minimizing dissections when treating severely calcified infrapopliteal lesions.

Introduction of the Shockwave S^4 IVL catheter allowed for expanded treatment of BTK lesions due to a smaller crossing profile and balloon diameters relative to the M^5 catheter. Adams et al recently analyzed a cohort of patients from the PAD III Observational Study (OS) with calcified BTK disease treated with the S^4 IVL catheter [11]. A total of 101 patients with 114 calcified infrapopliteal arteries were enrolled at 15 sites and were followed through discharge. This study included a challenging patient and lesion cohort with 69% of patients presenting with CLI and 35% with CTO lesions. The continued safety and effectiveness of peripheral IVL was demonstrated as 99% of lesions achieved a residual stenosis < 50% with no occurrences of serious angiographic complications at the end of the procedure, regardless of BTK lesion location.

3.1.3 Mini S IVL Catheter

The Mini S catheter is designed to leverage the same safety and effectiveness of IVL balloon catheters (M^5 and S^4) but represents a low-profile option with a distally-shifted emitter that can be used in sub-total occlusions with extremely narrow crossing channels where other devices may be challenged today.

The Shockwave Mini S Peripheral IVL Catheter has equivalent base materials and similar technological characteristics as the predicate device Shockwave S^4 Peripheral IVL Catheter. The Mini S and S^4 IVL Catheters have similar emitter designs that deliver unfocused intermittent acoustic pulses at the same pulse rate and treatment frequency at low treatment pressures. Sonic output mapping of the Mini S and S^4 IVL Catheters demonstrate that the average sonic output emitted by both devices have similar peaks and distribution and are within the same magnitude and standard deviation. These parameters have shown to be effective in treating calcified lesions with the S4 IVL Catheter and are applicable to the Mini S given the demonstrated equivalence.

Human cadaveric studies were conducted to assess the Mini S trackability, ability to cross and modify calcium, the visibility of the emitter band under fluoroscopy, and interaction with ancillary devices. The device was found to have an acceptable level of pushability/trackability, deliverability/crossability, emitter visibility, catheter working length and overall durability. These cadaver labs provided confirmation that Mini S IVL catheter functioned as intended by modifying calcium to allow for further treatment at the physician's discretion. Additional information regarding the pre-clinical studies can be found in the Investigator Brochure (IB 65349).

3.2 Study Rationale

The Mini S Feasibility study is being conducted to assess the safety and performance of the Shockwave Medical Mini S Peripheral IVL System for the treatment of heavily calcified, stenotic peripheral arteries.

4.0 STUDY DEVICE / TEST ARTICLE DESCRIPTION

4.1 Mini S Peripheral IVL Catheter

The Shockwave Mini S 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 dilatation of a peripheral artery stenosis. The Mini S IVL Catheter comprises a distal lithotripsy emitter for the localized delivery of pulsatile mechanical energy.

The Mini S IVL Catheter shaft contains a lumen to pressurize and flush the catheter, a guidewire lumen, and a lithotripsy emitter. The lumen is used to pressurize and flush the catheter with saline. The guidewire lumen enables the use of a 0.014" (0.36mm) guidewire to facilitate advancement of the catheter to and through the target stenosis. The system is designed as 'Over-the-wire' (OTW) with 150cm shaft working length. The emitter is positioned at the distal end of the catheter for delivery of pulsatile mechanical energy. The Mini S Catheter has a hydrophilic coating on the distal end designed to increase lubricity during advancement of the catheter to the treatment site. The emitter is radiopaque to facilitate catheter visibility under fluoroscopy and it is surrounded by an IVL Window that allows for the transmission of pulsatile mechanical energy. The proximal hub has three ports: one to pressurize and flush the system, one for guidewire lumen, and one for connection to the IVL Connector Cable. Refer to **Figure 1** below for IVL Catheter components.

The Mini S Peripheral IVL Catheter is available in two configurations: Standard and Flex. For easy identification, Standard has a blue shaft extrusion color and Flex has a yellow shaft. The Mini S Standard has a 15 cm distal segment, and the Flex has a 25 cm distal segment for more flexibility. The IVL Catheter is compatible with a 5Fr sheath and has a working length of 150cm. Both configurations will be evaluated in the Mini S Feasibility study.

The Mini S IVL Catheter is part of the Peripheral IVL System. The system consists of the IVL Catheter, an IVL Connector Cable and an IVL Generator. The Mini S IVL Catheter is to be used exclusively with the IVL Generator and its accessories. The IVL Generator and Connector Cable are not investigational; they are supplied non-sterile and are reusable. Refer to the *Shockwave Medical, Inc. IVL Generator and Connector Cable Operator's Manual* for preparation, operation, warnings and precautions, and maintenance of the IVL Generator and 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. Refer to the Instructions for Use (IFU) for a complete product description.

4.1.1 Mini S IVL Catheter Design Modification

The Mini S IVL Catheter has incorporated a design modification as part of continuous improvement. Two modifications were made to the Mini S IVL Catheter, the distance between the emitter and the distal tip and the shaft extrusion color. The emitter to distal tip length has been shortened on both configurations, Standard and Flex. A shorter distance between the emitter and the distal tip optimized energy delivery to facilitate crossing. There is no change to the energy profile or sonic output specification. The shaft extrusion color for Flex has been

changed from blue to yellow to allow for easier identification of both configurations during the manufacturing process and during use. The Standard configuration remains blue. The modifications do not alter the intended use or principles of operation, and the changes do not introduce new hazards which had not been previously addressed. More information regarding these design modifications to the Mini S IVL Catheter can be found in the Investigator Brochure (IB 65349).

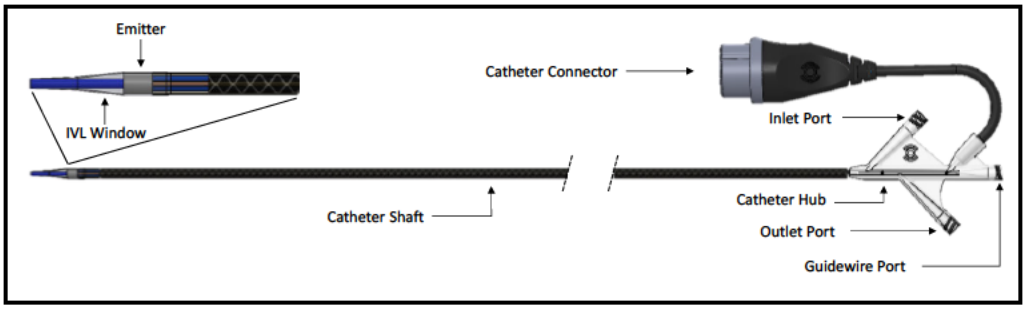

Figure 1. Shockwave Mini S Peripheral IVL Catheter

4.2 Indication for Use

The Mini S IVL Catheter is intended for lithotripsy-enhanced catheter dilatation of lesions, including calcified lesions found in the peripheral vasculature, such as the iliac, femoral, ilio-femoral, popliteal, infra-popliteal, and renal arteries. The Mini S IVL Catheter is not for use in the coronary or cerebral vasculature.

5.0 STUDY OBJECTIVES

The objective of this study is to assess the safety and performance of the Shockwave Medical Mini S Peripheral IVL System for the treatment of heavily calcified, stenotic peripheral arteries.

5.1 Safety Endpoints

The safety endpoints for this study include:

- **PRIMARY: Major Adverse Events (MAE)** at 30 days defined as a composite of:
    - Cardiovascular death
    - Clinically-driven target lesion revascularization (CD-TLR)
    - Unplanned target limb major amputation (above the ankle)
- **Serious angiographic complications** defined as flow-limiting dissection (≥ grade D), perforation, distal embolization, or acute vessel closure as assessed by the angiographic core lab.
- **MAE** at 6 and 12 months (as a composite and individual components)

5.2 Performance Endpoints

The performance endpoints are listed below. Device endpoints will be reported for all Mini S IVL Catheters.

- **PRIMARY: Technical Success** defined as *final* residual stenosis ≤50% without flow-limiting dissection (≥ Grade D) of the target lesion by angiographic core lab.
- **IVL Technical Success (post-dil)** defined as *post-dilatation* residual stenosis ≤50% without flow-limiting dissection (≥ Grade D) of the target lesion by angiographic core lab (measured immediately following mandatory post-dilatation).
- **IVL Device Success** defined as the ability to deliver, advance across the target lesion, pressurize, pulse, flush and retrieve the Mini S IVL Catheter.
- **Technical Success (final)** defined as *final* residual stenosis ≤30% without flow-limiting dissection (≥ Grade D) of the target lesion by angiographic core lab.
- **Primary Patency** at 12 months defined as:
    - Above the knee lesions: freedom from ≥50% restenosis as determined by Duplex Ultrasound (DUS) and freedom from Clinically-Driven Target Lesion Revascularization (CD-TLR)
    - Below the knee lesions: freedom from both total occlusion (100% diameter stenosis by DUS) in all of the target lesions in a flow pathway, as well as a CD-TLR

6.0 STUDY DESIGN

The Mini S Feasibility study is a pre-market, prospective, multi-center, single-arm feasibility study of the Shockwave Mini S Peripheral IVL System to treat heavily calcified, stenotic peripheral arteries.

6.1 Regulatory Status

Per ISO 14155:2020 (Annex I, Section 1.2), the Mini S Feasibility study is a pre-market study defined as a clinical investigation carried out before market approval of the investigational device.

6.2 Clinical Development Stage

Per ISO 14155:2020 (Annex I, Section 1.3), the medical device being used in the Mini S Feasibility study is in the pilot stage. In keeping with this development stage, the Mini S Feasibility study will evaluate the limitations and advantages of the Mini S IVL catheter and will capture preliminary information to adequately plan further steps of device development, including needs for design modifications or parameters for a pivotal clinical investigation.

6.3 Type of Clinical Investigation

Per ISO 14155:2020 (Annex I, Section 1.4), the Mini S Feasibility study is considered to be an exploratory clinical investigation that does not have pre-specified primary hypotheses, but may be used to generate hypotheses to be confirmed in subsequent clinical investigations. Per ISO 14155:2020 (Annex I, Section 1.5), it is an early feasibility study in which the Mini S IVL catheter is being evaluated for the first time in human subjects.

6.4 Number of Sites

Up to 6 sites in Australia and New Zealand will participate in the study.

6.5 Number of Subjects

Up to 50 subjects with a minimum of 10 BTK lesions treated with moderate to severely calcified peripheral artery disease (PAD) with a target lesion located in a native, *de novo* superficial femoral, popliteal or infrapopliteal artery will be enrolled. Up to two (2) target lesions may be treated per subject.

6.6 Clinical Study Duration

Enrollment is anticipated to last approximately six (14) months. Study subjects will be followed through hospital discharge, 30 days, 6 and 12 months post-procedure. Total anticipated study duration is 26 months.

7.0 STUDY PROCEDURES

7.1 Screening

Patients presenting to the institution with known peripheral artery 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 performed according to the institution's standard of care. If all angiographic eligibility criteria are met, the patient is considered to be enrolled once a 0.014" guidewire has crossed the target lesion and the Mini S peripheral IVL catheter has been inserted over the guidewire and into the body. A subject is considered an angiographic screen failure if they do not meet angiographic eligibility criteria. Patients who screen fail will be documented as such in the electronic data capture (EDC) system.

7.2 Subject Selection

7.2.1 Inclusion Criteria

Subjects are required to meet all of the following inclusion criteria in order to be enrolled in the study. For lesion characteristics, each target lesion must meet eligibility. A maximum of two (2) target lesions may be treated per subject; target lesions may be in the same limb or in different limbs.

General Inclusion Criteria

1. Age of subject is ≥ 18 years.
2. Subject is able and willing to comply with all assessments in the study.
3. Subject or subject's legal representative has been informed of the nature of the study, agrees to participate, and has signed the approved consent form.
4. Estimated life expectancy > 1 year.
5. Rutherford Clinical Category 2, 3, 4 or 5 of the target limb(s).

Angiographic Inclusion Criteria

6. One or two target lesion(s) located in a native de novo superficial femoral, popliteal or infrapopliteal artery (above the ankle joint), in one or both limbs.

7. Target lesion reference vessel diameter (RVD) between 2.0 mm and 7.0 mm by investigator visual estimate.
8. Target lesion stenosis ≥70% (for vessels below the knee, defined as P3 to the ankle joint) or ≥90% (for vessels above the knee) by investigator visual estimate.
9. Target lesion length is ≤150 mm by investigator visual estimate. Target lesion can be all or part of the 150 mm treated zone.
    - Tandem lesions (lesions < 3 cm apart) are allowed if the total treated area covers the entire diseased segment. Total treated area is defined as the area treated by any device (pre-dilatation, IVL, post-dilatation, or destination therapy). Each tandem lesion/diseased segment is considered one target lesion.
    - If these segments are treated independently (i.e., no PTA treatment between two lesions) then this is considered two separate target lesions.
10. 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

Subjects who meet any of the following exclusion criteria may not be enrolled in the study:

General Exclusion Criteria

1. Rutherford Clinical Category 0, 1 and 6 (target limb).
2. History of endovascular or surgical procedure on the target limb within the last 30 days, or planned within 30 days of the index procedure, with the exception of toe amputation. Note: inflow treatment of non-target lesions is allowed providing successful treatment.
3. Subject in whom antiplatelet or anticoagulant therapy is contraindicated.
4. Subject has known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-treated.
5. Subject has known allergy to urethane, nylon, or silicone.
6. Myocardial infarction within 60 days prior to enrollment.
7. History of stroke within 60 days prior to enrollment.
8. Subject has acute or chronic renal disease with eGFR <30 ml/min/1.73 m^2 (using CKD-EPI formula), unless on renal replacement therapy.
9. Subject is pregnant or nursing.

10. Subject is participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint.
11. 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.
12. Covid-19 diagnosis within 30 days.
13. Planned use of cutting/scoring balloons, re-entry or atherectomy devices in target lesion(s) during the index procedure.
14. Planned major amputation of target limb.
15. Acute limb ischemia.
16. Occlusion of all the inframalleolar outflow arteries/vessels (i.e., desert foot).
17. Subject already enrolled into this study.

Angiographic Exclusion Criteria

18. Failure to successfully treat clinically significant inflow lesions in the ipsilateral iliac, femoral, or popliteal arteries, defined as ≤30% residual stenosis with no serious angiographic complications (e.g. embolism).
19. Failure to successfully treat significant non-target infrapopliteal lesions, if treated prior to treatment of target lesion(s). Successful treatment is defined as obtaining ≤50% residual stenosis with no serious angiographic complications (e.g., embolism).
20. Target lesion includes in-stent restenosis.
21. Evidence of aneurysm or thrombus in target vessel.
22. No calcium or mild calcium in the target lesion.
23. Target lesion within native or synthetic vessel grafts.
24. 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 14155:2020 and comply with the ethical principles of ICH/GCP and 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
- The informed consent process should be documented by the Investigator completing the consenting process in the subject's institutional medical record

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. Schedule of Events and Evaluations

Assessment	Screening / Baseline	Enrollment and Procedure	Discharge[1]	30 Days (-7/+14 days)	6 Months (180±30 days)	12 Months (365±30 days)	Pre-TLR
Eligibility	√						
Informed Consent[2]	√						
Medical History	√						
Physical Exam	√			√	√	√	
eGFR	√						
Pregnancy Test	√[3]						
Medications	√		√	√	√	√	
ABI or TBI	√[4]			√	√	√	
Rutherford Category	√			√	√	√	
Angiogram		√					√[5]
DUS						√	
Adverse Events		√	√	√	√	√	√

TLR = target limb revascularization; ABI = ankle-brachial index; TBI = toe-brachial index
1. Within 12-24 hours post procedure or prior to hospital discharge, whichever occurs first
2. Consent to be obtained within 30 days prior to procedure.
3. Within seven (7) days of the procedure for women of child-bearing age.
4. Within 60 days prior to procedure.
5. Angiographic images acquired as standard of care prior to the TLR should be submitted to the core lab.

7.5 Medications

Anticoagulation/antiplatelet medications should be administered according to the 2017 European Society of Cardiology (ESC) and European Society of Vascular Surgery (ESVS) PAD guidelines [20] and the 2016 American College of Cardiology (ACC) and American Heart Association (AHA) PAD guidelines [5].

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 ankle-brachial index (ABI) and toe-brachial index (TBI), which can be completed within 60 days of the procedure, and a pregnancy test which must be done within seven (7) days of the procedure for women of child-bearing age. 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
- eGFR (if needed, for patients with acute or chronic renal disease)
- Review of anticoagulation/antiplatelet medications
- ABI or TBI of target limb (at rest; use same test for subject throughout study)
- Rutherford Category of target limb
- Urine pregnancy test if female of child-bearing age

Note: If treatment of two target lesions is planned across both limbs, the RC category, ABI, and TBI for each limb must be assessed. If ABI cannot be assessed due to non-compressible vessels, this should be documented. If TBI is used, subject should have TBI at each follow-up visit.

7.7 Index Procedure

The IVL procedural flow diagram is described in the steps below and illustrated in Figure 2. All devices used during the index procedure should be recorded including IVL catheters and adjunctive

devices (if required). Up to two (2) target lesions may be treated per subject. If the distal portion of the target lesion extends beyond the ankle joint, treatment using the Mini S IVL Catheter is allowed if the Investigator deems it clinically necessary to optimize the procedure outcome.

For the first 10 consecutively enrolled subjects, the Flex configuration of the Mini S IVL Catheter should be used first; cross-over to the Standard configuration is allowed if needed per the IVL procedural steps outlined below. For the next 10 consecutively enrolled subjects, the Standard configuration should be used first with crossover to Flex if needed. For subjects enrolled after the first 20 subjects, the Mini S configuration may be chosen at the Investigator's discretion. Cross-over to the other configuration is allowed if needed per the IVL procedural steps outlined below.

Information on usability will be collected to help understand how operators perceive information from the Mini S IVL Catheter, interpret the information and make decisions about what to do, and how to manipulate the device.

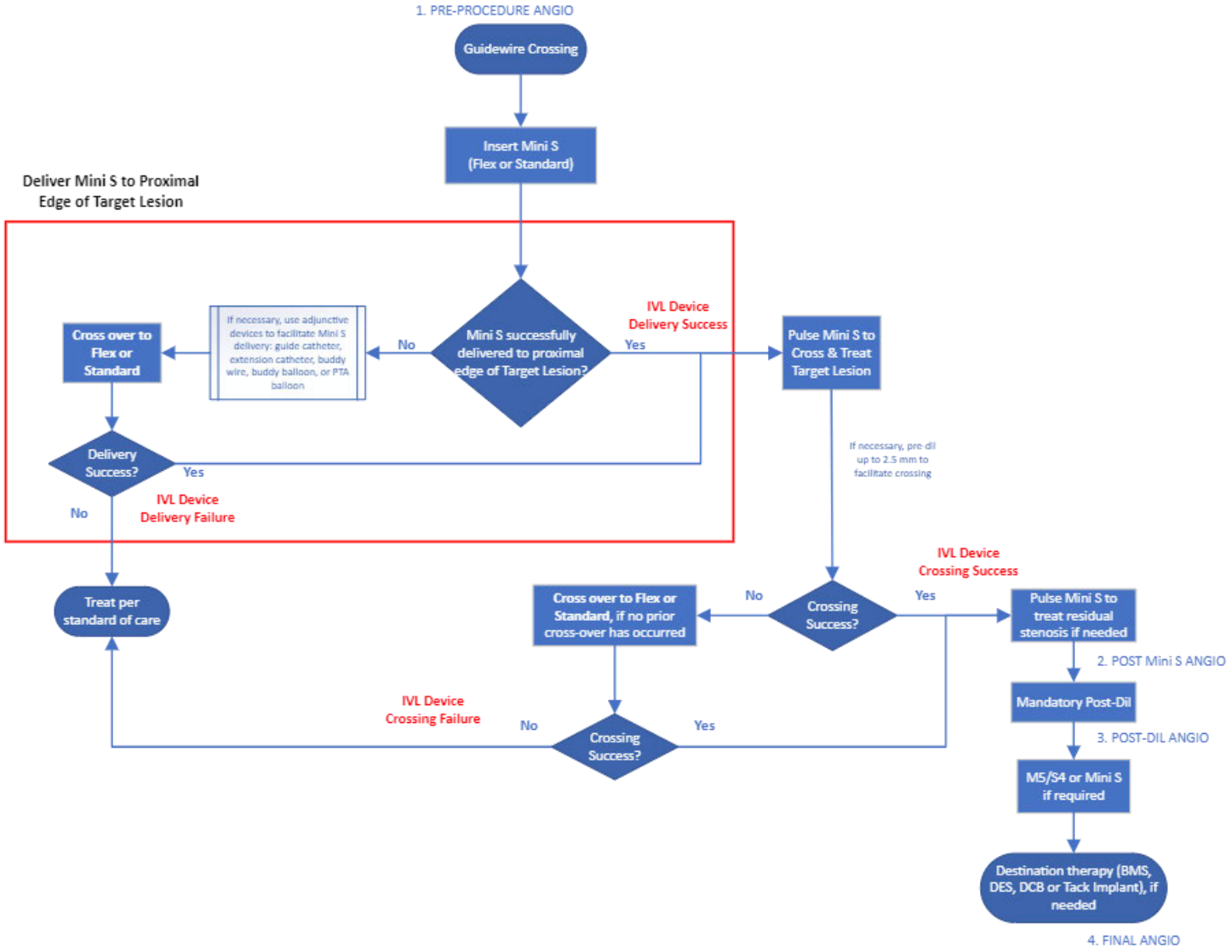

Figure 2. Mini S IVL Treatment Algorithm

7.7.1 Procedural Imaging Requirements

An angiographic cine will be obtained at four (4) timepoints for each target lesion as follows:

1. Pre-procedure (include run-off the foot)
2. Post-Mini (immediately following treatment with Mini S and before post-dilatation)
3. Post-Dil (following mandatory post-dilatation)
4. Final (end of procedure, include run-off to the foot)

If any non-target lesions are treated, an additional cine will be obtained prior to IVL treatment of any target lesion(s) to ensure no serious angiographic complications have occurred and that the patient still meets criteria to be enrolled. All angiographic images must be submitted to the core lab for analysis. If intravascular imaging (including IVUS or OCT) is performed as standard of care, images from the four timepoints (pre-procedure, post-Mini, post-Dil and final) should be submitted to the Sponsor for analysis.

Core lab training materials will be provided with detailed instructions on the image acquisition process.

7.7.2 Assessment of Calcification

To meet eligibility, there must be 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.

The 1st required angiographic cine (Pre-procedure) should be acquired following assessment of calcification.

7.7.3 Treatment of Non-Target Lesions

Non-target lesions should be treated successfully prior to treatment of the target lesion(s) whenever possible. Non-target lesions distal to the target lesion(s) or found after target lesion is treated may be treated after the target lesion(s).

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.

Clinically significant inflow lesions in the ipsilateral iliac, femoral, or popliteal arteries must be treated with ≤30% residual stenosis and no serious angiographic complications (e.g. embolism). Significant non-target infra-popliteal lesions should be treated with ≤50% residual stenosis with no serious angiographic complications (e.g., embolism). If there are serious angiographic complications following treatment of non-target lesions prior to insertion of the Mini S IVL Catheter, the patient should not be enrolled.

7.7.4 Definition of Enrollment

The definition of enrollment is when the subject signs informed consent, meets all general and angiographic eligibility criteria, a 0.014" guidewire has crossed the target lesion, and the Mini S IVL catheter has been inserted over the guidewire and into the body.

7.7.5 Catheter Delivery & Crossover (if required)

If the Investigator is able to pass a guidewire but is unable to deliver the Mini S IVL catheter to the proximal edge to the target lesion, an adjunctive tool may be used prior to re-insertion of the Mini S IVL Catheter. Allowable adjunctive tools include guide catheter, guide extension catheter, buddy wire or buddy balloon, and PTA balloon. Atherectomy, cutting/scoring balloons, and specialty crossing devices should not be used. All adjunctive tools used during the procedure should be documented.

If the Mini S IVL Catheter still cannot be delivered to the proximal edge of the target lesion, the user may cross over to the other Mini S catheter configuration (Standard or Flex depending on which configuration was used first). All crossovers should be documented.

If the user is unable to advance any Mini S IVL Catheter to the proximal edge of the target lesion after crossing over to the alternate Mini S configuration, this is considered an **IVL Device Failure**. Treatment should continue per standard of care for the subject.

7.7.6 Pre-IVL Dilatation of Target Lesion & Crossover (if required)

If the operator is unable to cross the Mini S IVL Catheter through the entire length of the target lesion, a standard PTA balloon up to 2.5 mm may be used for pre-dilatation of the target lesion prior to treatment with the Mini S IVL Catheter. All efforts should be made to pass the Mini S IVL Catheter prior to use of a standard PTA balloon.

If the operator is unable to pass the Mini S IVL Catheter after pre-dilatation, the operator may attempt to cross with the alternate Mini S configuration (crossover). Note: if the operator has already used the alternate configuration (prior crossover per Section 7.7.5), a second crossover is not permitted. All crossovers should be documented.

If the user is unable to advance any Mini S IVL Catheter across the target lesion, this is considered an **IVL Device Failure**. Treatment should continue per standard of care for the subject.

7.7.7 IVL Treatment

Once the Mini S IVL Catheter is placed in the target lesion area, the catheter must be pressurized to 4 atm to deliver one cycle of IVL pulses. Table 2 lists the pulsing sequence for the Mini S IVL Catheter. One cycle = 10 pulses. The catheter is able to deliver total of 12 cycles (120 pulses). Note that the generator is programmed to force a minimum pause time of 10 seconds following every cycle.

Following delivery of the first IVL cycle, record lesion response on fluoroscopy. Before delivering the next treatment cycle, open the outlet port and pressurize to 6 atm to flush the system with saline.

Repeat the steps above to deliver additional pulses of IVL. Multiple locations should be treated for long lesions. For optimal results, treat the entire lesion length with IVL; do not use "spot" IVL. **Caution:** Care must be taken not to exceed 120 pulses in the same segment.

Following initial treatment with the Mini S, the 2nd required angiographic cine (Post-Mini) should be acquired.

Table 2. Mini S IVL System Sequence Chart

	Mini S
Treatment Frequency	1 Pulse per Second
Maximum Number of Continuous Pulses (1 cycle)	10 Pulses
Minimum Pause Time (between cycles)	10 Seconds
Maximum Total Pulses Per Catheter	120 (12 Cycles)

7.7.8 Post-Dilatation (Mandatory)

Post-dilatation with a semi or non-compliant PTA balloon catheter must be completed at nominal pressure.

The physician should use a 1:1 balloon catheter to artery ratio and may dilate for several minutes. Follow the angiographic core lab guidelines to complete angiography showing all target lesions with reproducible landmarks for follow-up evaluation and assessment.

Following mandatory post-dilatation, the 3rd required angiographic image (Post-Dil) should be acquired.

7.7.9 Additional Target Lesion Treatment (if required)

Following mandatory post-dilatation, additional IVL treatment may be delivered if areas of non-dilatable residual stenosis > 50% remain. This may be done using the commercially available Shockwave M^5, M^{5+} (where applicable) or S^4 IVL catheters – or additional pulses with the same Mini S IVL catheter configuration used for treatment in section 7.7.7 may be delivered.

7.7.10 Destination Therapy

Destination therapy is allowed at the discretion of the Investigator. Destination therapy may include commercial IVL, bare-metal stent (BMS), drug-eluting stent (DES), drug coated balloon (DCB) or Tack implant.

A BMS, DES, DCB or Tack implant is allowed for the following PTA failures:

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

If this treatment is performed at the time of procedure, it is considered standard of care to maximize acute luminal gain and does not meet the definition of serious deterioration in the SAE definition (Section 10.1.2).

All dissection Type/Grade A, B, and C must be documented as an adverse event. Dissection Type/Grade D, E, and F must be documented as a SAE.

The 4th and final required angiographic cine should be acquired after all endovascular procedures on the target lesion are complete.

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:

- Review of anticoagulation/antiplatelet medications
- Adverse event assessment

7.8.2 30-Day Follow-Up

The following evaluations will be performed at **30 days** (-7/+14 days) post procedure:

- Physical examination
  - Vital signs
- ABI or TBI of target limb (at rest; keep consistent with screening)
- Rutherford Category of target limb
- Review of anticoagulation/antiplatelet medications
- Adverse event assessment

Note: If treatment of two target lesions is planned across both limbs, the Rutherford Category and ABI/TBI for each limb must be assessed. If ABI/TBI cannot be assessed due to non-compressible vessels, this should be documented.

7.8.3 6-Month Follow-Up

The following evaluations will be performed at **6 months** (180 +/-30 days) post procedure:

- Physical examination
  - Vital signs
- ABI or TBI of target limb (at rest; keep consistent with screening)
- Rutherford Category of target limb
- Review of anticoagulation/antiplatelet medications
- Adverse event assessment

Note: If treatment of two target lesions is planned across both limbs, the Rutherford Category and ABI/TBI for each limb must be assessed. If ABI/TBI cannot be assessed due to non-compressible vessels, this should be documented.

7.8.4 12-Month Follow-Up

The following evaluations will be performed at **12 months** (360 +/-30 days) post procedure:

- Physical examination
  - Vital signs
- ABI or TBI of target limb (at rest; keep consistent with screening)
- Rutherford Category of target limb
- Review of anticoagulation/antiplatelet medications
- Adverse event assessment
- Duplex ultrasound (DUS)

Note: If treatment of two target lesions is planned across both limbs, the Rutherford Category and ABI/TBI for each limb must be assessed. If ABI/TBI cannot be assessed due to non-compressible vessels, this should be documented.

7.8.5 Prior to Target Limb Revascularization

If a target limb revascularization procedure is performed during the follow-up period, angiographic images acquired as standard of care should be submitted to the core lab for purposes of adjudication.

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, adverse event and study exit/withdrawal forms should be completed. Physician assessment is required to determine if the cause of death was possibly or definitely related to the Mini S Peripheral IVL Catheter. 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. Associated regulatory bodies may also be required to be notified depending on local jurisdiction and relatedness to the study device and procedures.

8.0 BENEFITS AND RISKS

8.1 Benefits

There may be no additional benefit from participation since patients can receive IVL treatment with a commercially available device per standard of care. The study will provide safety and performance data associated with treatment of calcified arteries using the Mini S IVL Catheter. 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 device(s) used in the study procedure, including a complete list of contraindications, warnings, precautions, and potential adverse effects, please refer to the Instructions for Use (IFU) for the Mini S Peripheral IVL Catheter. It is important to ensure that the IFU referred to represents the generation of the device used in the study procedure. Unanticipated risks can occur.

Possible adverse effects are consistent with standard intravascular procedures. Risks identified as unique to the device and its use are outlined in the IFU for the Mini S Peripheral IVL Catheter. They include:

- Allergic/immunologic reaction to the catheter material(s) or coating
- Device malfunction or failure

8.3 Risks Associated with Participation in the Clinical Investigation

All assessments are considered to be standard of care but may be conducted more frequently to comply with the follow-up visit schedule. Non-invasive assessments at follow-up visits include physical exams, ABI/TBI, Rutherford Category assessments, and duplex ultrasounds. All pose minimal risk to the patient. For procedure-related risks, please refer to the current IFUs.

Risks associated with the management of privacy and confidentiality with the sharing of data exist for subjects participating in research studies. To mitigate these risks, each subject in the study will be assigned a specific study identification code that shares no identifiable factors with the Sponsor. Only hospital staff and the CRO will be privy to information that links the subject's identifiable information to this subject code. De-identified data (data that is attributed to the subject's study identification code) will be uploaded into a password protected Electronic Data Capture (EDC) system. This EDC can only be accessed by suitably trained and allocated members of the study team (site Investigators, Study Coordinators, personnel associated with the CRO and relevant personnel at the Sponsor organization).

8.4 Possible Interactions with Concomitant Medical Treatments

There are no known possible interactions within this study.

8.5 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
- Assignment of study identification code to protect privacy and ensure confidentiality
- Study monitoring
- Safety processes – protocol adverse event reporting requirements, CEC and DSM oversight, and safety reporting to regulatory authorities including Vigilance reporting
- Review of all device malfunctions and complaints by Quality. Risk acceptability thresholds and trend identification methods have been established, and actions will be taken if those are met.

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 post procedure.

Categorical variables will be summarized by the number of observations available, frequency, and percentage. Unless otherwise noted, missing data will be excluded from the denominator. Clinical outcomes analyzed at 30 days will be evaluated as categorical (binary) data. Exact confidence intervals will be generated for estimates of proportions.

Continuous variables will be summarized by the mean, standard deviation, median, minimum and maximum. Asymptotic confidence intervals will be generated for estimates of means.

9.2 Statistical analyses will be performed using SAS System® Version 9.4 or higher. Primary Endpoints

9.2.1 Primary Safety Endpoint

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

- Cardiovascular death
- Clinically-driven target lesion revascularization (CD-TLR)
- Unplanned target limb major amputation (above the ankle)

SAEs will be reviewed and adjudicated by the CEC. Only those adjudicated as MAEs will comprise the composite safety endpoint.

MAEs will be assessed on a per-subject basis.

9.2.2 Primary Performance Endpoint

Technical Success defined as final residual stenosis ≤50% without flow-limiting dissection (≥ Grade D) of the lesion by angiographic core lab.Primary Performance will be assessed on a per-lesion basis.

9.3 Sample Size Determination

Per ISO 14155:2020 (Annex I, Section 1.4), the Mini S Feasibility study is considered to be an exploratory clinical investigation that does not have pre-specified primary hypotheses. For feasibility studies, sample sizes between 12 and 50 have been recommended [21-25]. The sample size for the Mini S Feasibility study (up to n=50) is in keeping with these published recommendations.

9.4 Populations for Analysis

The primary analysis population will be the Intent-to-Treat (ITT) cohort which includes all enrolled subjects.

9.5 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 who do not experience the event in question 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. All adverse events will be coded using MedDRA.

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)

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 medical device and whether anticipated or unanticipated.

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

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

Note: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

10.1.2 Serious Adverse Event (SAE)

Adverse event that led to any of the following

a) death,

b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function including chronic diseases, or

3) in-patient or prolonged hospitalization, or

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

c) fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment.

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

10.1.3 Adverse Device Effect (ADE)

Adverse event related to the use of an investigational device.

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 use error or from intentional misuse of the investigational medical device.

Note: This includes "comparator" if the comparator is a 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 Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

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".

.

- 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, usability, safety or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

Note: This definition includes device deficiencies related to the investigational medical device or the comparator.

Device Malfunction is a failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or Clinical Investigation Plan (CIP), or Investigator Brochure (IB).

10.3.2 Reporting

All device deficiencies and malfunctions will be documented on the case report form and reported to the Study Sponsor within 2 business days 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 reports, 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 2 business days 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 local IRB/EC policies. The Investigator should forward a copy of this report to the Study Sponsor and file in the site regulatory binder.

The Clinical Events Committee (CEC) will review and adjudicate SAEs. See section 13.1 for information on the CEC.

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 2 business days after the designated study site personnel first learns of the event. All SADEs should be reported to the IRB/EC in accordance with their local requirements.

10.4.5 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 2 business days after the Investigator first learns of the event. All USADEs should be reported to the IRB/EC in accordance with their local requirements.

10.4.6 AE and Device Deficiency Reporting Time Frames

Table 3 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 Reporting Adverse Events

Type of Event	Process
Device deficiencies (including malfunctions)	Submit AE CRF in EDC within 2 business days after the designated study site personnel first learns of the event and to the local IRB/EC (if required) within the IRB/EC required timeframe.
Serious adverse events (SAE, SADE)	Submit AE CRF in EDC within 2 business days after the designated study site personnel first learns of the event and to the local IRB/EC within the IRB/EC required timeframe.
Unanticipated serious adverse device effect (USADE)	Submit AE CRF in EDC as soon as possible, but no later than 2 business days, to the Study Sponsor after the designated study site personnel first learns of the event and to the local IRB/EC within the IRB/EC required timeframe.
Non-serious adverse events (AE, ADE)	Submit AE CRF in EDC to the Study Sponsor as soon as possible after study personnel has become aware of the event, and to the local 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, ICH/GCP, Declaration of Helsinki, and ISO 14155:2020 requirements 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 before submitting to the local IRB/EC for approval. 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 submit all amendments to the local IRB/EC and regulatory agency to obtain to obtain written approval, before implementing changes.

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's designated Contract Research Organization (CRO). See Section 2.0 for the independent CRO designated for this study. 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 the use of remote monitoring (if allowed per institutional or jurisdictional policies) 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.

Major deviations include those that involve the primary endpoint, the informed consent process, 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 within the applicable study management system. 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, and the site has been suitably trained by the sponsor in the use of the investigational device.

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. A final study report will be completed no later than 12 months after study completion, even if the clinical study was terminated prematurely.

12.7 Audits / Inspections

Shockwave Medical, regulatory agencies, and 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, report generation, and primary system for imaging vendor. 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.

Data collected during the study includes demographic data, baseline health information (including relevant past medical history), information regarding use of the investigational product, diagnostic imaging, and questionnaires regarding subject symptoms related to their vascular disease.

Data (de-identified) collected will be uploaded by the investigator (or their designee) into a password protected Electronic Data Capture (EDC) system. This EDC will be administered by Shockwave Medical in Santa Clara, California. In cases where certain types of data (such as diagnostic images) cannot be uploaded to the EDC, such data will be transferred using a secure File Transfer Protocol (FTP) link that is generated by the investigative site. De-identified data may be securely shared with the CEC for adjudication of adverse events and accessed by trained members of the CEC or the CEC management team.

For this study, [redacted], is being used to record de-identified clinical trial data as well as used as the primary system for the imaging vendor. As such all data collected for this study will be stored in [redacted]. A copy can be provided by the vendor or sponsor upon request .

Shockwave Medical intends to utilize the data obtained from the study for commercial uses including publication and/or presentation of results at conferences and congresses, regulatory agency submissions (including but not limited to United States Food and Drug Administration [FDA], Australian Therapeutic Goods Administration [TGA] and CE), 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. Data will only be presented in aggregate; individual data will not be presented.

12.9.1 Data Guardianship

The data collected will be managed according to the study specific Sponsor Data Management Plan through the life cycle of the study and any specified data retention periods (see section 12.9.5). The participant and/or individuals/or others, including Indigenous, geographic and demographic specific communities, groups, and interests in relation to data will be recognised. Furthermore, the participant and/or individuals, others, or groups may be involved in the governance of their data. Data collected will also be subject to local data management guidelines as specified by local IRB/EC.

During this study, data will be collected and stored in two formats to maintain the welfare, safety and privacy of subjects. Data will be collected and managed in the following formats:

Identifiable information

Identifiable information is any data that could identify subjects (e.g. name, date of birth, or address). This information is used to complete study specific documents that are held at study sites, and the following people may have access to a subject's identifiable information:

- Research team members, including study doctor(s) and Research Coordinator(s).
- Lab techs, ultrasound techs and staff at radiology providers where diagnostic tests and study procedures are performed – they will collect and report any screening and follow up tests.

- Study monitor (an authorized representative of the Sponsor will be provided with access to review medical records to check the accuracy of the information.
- The Sponsor and its representatives, in the instance a compensation claim for study-related injury. Identifiable information is required in order to assess any such claims.
- The Sponsor, Ethics Committees, or government agencies from this country or overseas (e.g. United States Food and Drug Administration (US FDA)), if the study or site is audited. Audits are done to make sure that subjects are protected, the study is run properly, and the data collected is correct.
- A subject's doctors or physicians, if a study test gives an unexpected result (incidental finding) that could be important for managing or maintaining health. This allows appropriate follow-up to be arranged.

De-identified information

To make sure a subject's personal information is kept confidential, information that identifies subjects will not be included in any study information sent to the Sponsor. Instead, subjects will be identified by a unique study number, also known as a "code". The research team will keep a list linking a subject's code with their name, so that they can be identified by their coded data if needed. The following groups may have access to a subject's de-identified and coded information as this will be sent and stored overseas:

- The Sponsor, for the purposes of this study.
- People and companies working with or for the sponsor, for the purposes of this study (this may include approx. 15 people across 5 organizations; Sponsor, Core lab providers (where imaging analysis occurs), CEC, DSM, and the Contract Research Organization (CRO).
- Regulatory or other governmental agencies worldwide.

12.9.2 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. Subject names will not be released to Shockwave Medical at any stage of the study.

12.9.3 Transmission of Data

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 and source information associated with adverse events) must be sent to Shockwave Medical (if applicable to local site regulations) and/or verified/retrieved from the Investigator during monitoring visits. Data sent to Shockwave Medical will be de-identified and done so utilizing a secure web-based system.

12.9.4 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 by Shockwave Medical or its designee 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.

12.9.5 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 under the custodianship of the Sponsor 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, including SAEs, as described in the CEC charter.

The CEC will be managed by [redacted]. 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 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. Members have expertise in peripheral endovascular procedures, are experienced in the conduct of controlled clinical trials and have knowledge of bioethics and integrity related to the duties and responsibilities to be performed.

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. Events to be adjudicated include death, MAEs, revascularizations, and amputations. The CEC will also adjudicate relationship to the study device and study procedure according to the following classifications: definitely related, probably related, possibly related, unlikely related and not related.

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. In addition, the CEC Charter will include the number of members, responsibilities, CEC meeting procedures, and meeting frequency.

13.2 Independent Data and Safety Monitor (DSM)

An independent Data and Safety Monitor (DSM) will be responsible for reviewing study data, monitoring for excessive occurrence of adverse events and making recommendations to Shockwave Medical regarding safety issues and risks to research participants as well as the continuing validity and scientific merit of the study. The DSM will make recommendations including (but not limited to) modification of the protocol, continuation/discontinuation of enrollment, and/or temporary suspension of enrollment in the trial. The DSM will be a physician with required training, experience and expertise in the field of peripheral endovascular procedures and in the conduct of clinical trials.

The independent DSM will conduct reviews of safety data in accordance with the protocol, local regulations where applicable, ICH E6: Good Clinical Practice (GCP) guidelines, and ISO14155:2020. At regular intervals during the course of the study, the DSM shall:

- Evaluate all adverse events with regard to interim results of the study for evidence of undue risk to research subjects and/or safety concerns.
- Provide recommendations regarding continuation/discontinuation of enrollment, and/or temporary suspension of enrollment due to safety concerns.
- Evaluate study progress with projections of recruitment and timelines for study milestones. This also includes evaluation of any significant trends of performance that may influence the safety or conduct of the study.
- Advise the Sponsor and other responsible parties on potential protocol-related concerns regarding procedures, definitions or endpoints, allowing timely notification of regulatory authority for protocol revisions.

In addition to regularly scheduled data reviews, the DSM will be notified immediately if any of the following events occur: any in-hospital death associated with the index procedure, any investigational device malfunction contributing to a serious adverse event, or failure to retrieve the investigational device.

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. Sponsor will provide insurance for this study.

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

As per the Data Management Section 12.9, 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 such as regulatory or auditing agencies (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. Data will not be provided to third party agencies that are not associated with the commercial or research operations of the Sponsor.

15.0 DEFINITIONS and ABBREVIATIONS

15.1 Study Definitions

Abrupt or Acute Closure: Angiographic documentation of significantly reduced flow due to mechanical dissection, thrombus, or severe vessel spasm in the treatment area.

Acute Limb Ischemia: A sudden decrease in limb perfusion that causes a potential threat to limb viability (manifested by ischemic rest pain, ischemic ulcers, and/or gangrene) in patients who present within two weeks of the acute event.

Adverse Device Effect (ADE): Adverse event related to the use of an investigational 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 the investigational medical device.

Note: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Note: This includes "comparator" if the comparator is a medical device.

Adverse Event (AE): 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 medical device and whether anticipated or unanticipated.

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

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

Note: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

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

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.

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

Calcification Classification (PARC): Calcification will be assessed by the angiographic core lab according to the Peripheral Academic Research Consortium (PARC) definition [26].

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

Clinical Events Committee (CEC): Committee responsible for establishing and implementing decision rules, definitions for the adjudication of clinical events using the data collected in the study, and for providing unbiased adjudication of clinical events.

Clinically Relevant Target Lesion Occlusion: Clinically relevant restenosis defined as the presence of a 50% or greater narrowing accompanied by a judgement of clinical relevance. Clinical relevance adjudicated by independent CEC based on worsening of Rutherford score, non-healing of wounds, ABI drop of ≥0.15, TBI drop of ≥0.10, each as compared to post-procedural outcomes, or absolute toe pressure ≤30 mmHg.

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.

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).

Data and Safety Monitor (DSM): Data and Safety Monitor will be responsible for reviewing study data, monitoring for excessive occurrence of adverse events and making recommendations to Shockwave Medical regarding safety issues and risks to research participants as well as the continuing validity and scientific merit of the study.

Death: (divided into 2 categories)

Cardiovascular 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 cardiovascular cause cannot be excluded

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

Device Deficiency: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

Note: This definition includes device deficiencies related to the investigational medical device or the comparator.

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: Minor radiolucent areas within the lumen without impairment of flow or persistent dye staining after contrast runoff.

Type B: Luminal flap that is radiolucent and runs parallel to the vessel wall with contrast injection but without impairment of flow or persistent dye staining after contrast runoff.

Type C: Contrast appears outside of the vessel lumen as an “extraluminal cap”, the staining appears even after contrast clears off the lumen.

Type D: Spiral radiolucent luminal filling defects, often persistent staining after contrast clears from the vessel.

Type E: New and persistent filling defects in the vessel lumen.

Type F: Lesions that progress to impaired flow or total occlusion.

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.

Intravascular Lithotripsy (IVL): 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:

- cardiovascular death
- target lesion revascularization
- Unplanned target limb major amputation (above the ankle)

Perforation: Puncture of an arterial wall.

Restenosis: Reoccurrence of narrowing or blockage of target lesion.

Rutherford Classification of Critical Limb Ischemia:: Clinical staging system for describing PAD. It includes 7 categories:

Grade	Category	Clinical Description
0	0	Asymptomatic
I	1	Mild claudication
I	2	Moderate claudication
I	3	Severe claudication
II	4	Ischemic rest pain
III	5	Ischemia ulceration not exceeding ulcer of the digits of the foot
IV	6	Severe ischemic ulcers or frank gangrene

ACC/AHA/SCIA/SIR/SVM 2018 Appropriate Use Criteria for Peripheral Artery Intervention – Bailey et al. 2019)

Serious Adverse Device Effect (SADE): Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse even.

Serious Adverse Event (SAE): Adverse event that led to any of the following:

- death,

- serious deterioration in the health of the subject, user, or other persons as defined by one or more of the following:
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function including chronic diseases, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to body structure or a body function,
    - foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment.

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

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.

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

Unanticipated Serious Adverse Device Effect (USADE): Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

Wound: Foot ulcer or gangrene. After debridement and/or minor amputation, a wound is characterized as a healed wound when it is completely epithelialized.

15.2 List of Abbreviations

ABI	Ankle-Brachial Index
ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Association
BTK	Below-the-Knee
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLI	Critical Limb Ischemia
CRF	Case Report Form
CRO	Contract Research Organization
CTA	Computed Tomography Angiogram
CTO	Chronic Total Occlusion
DCB	Drug-Coated Balloon
DES	Drug-Eluting Stent
DSM	Data and Safety Monitor
DUS	Duplex Ultrasound
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EC	Ethics Committee
ESC	European Society of Cardiology
ESVS	European Society of Vascular Surgery
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IFU	Instruction for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization

ITT	Intent-to-Treat
IVL	Intravascular Lithotripsy
IVUS	Intravascular Ultrasound
MAE	Major Adverse Event
MALE	Major Adverse Limb Event
MDR	Medical Device Reporting
MRA	Magnetic Resonance Angiography
OCT	Optical Coherence Tomography
OTW	Over-the-Wire
PAD	Peripheral Artery Disease
PARC	Peripheral Academic Research Consortium
POD	Post-Operative Death
PTA	Percutaneous Transluminal Angioplasty
RC	Rutherford Category
RVD	Reference Vessel Diameter
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TBI	Toe-Brachial Index
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
USADE	Unanticipated Serious Adverse Device Effect

16.0 REFERENCES

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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	8/30/2021	22353	Initial release.	Clinical
B	9/23/2021	22516	• Added Secondary Endpoint: primary patency at 12 months. • Added Independent DSM section 13.2 and contact info. • Added additional CEC language. • Added BTK lesion percentage. • [redacted]. • Added Data Guardianship section 12.9.1. • Added CEC definition and DSM definition and abbreviation.	Clinical

Revision	Release Date	DCO #	Reason(s) for Revision	Doc Owner
C	7/27/2022	24247	• Expanded enrollment to up to 50 with a minimum of 10 BTK lesions treated. • Added Mini S IVL Catheter Design Modification Section 4.1.1. • Updated anticipated enrollment and study duration in Section 6.6. • Secondary endpoint changes: IVL Technical Success (Mini) removed and combined IVL Delivery Success and IVL Device Crossing with IVL Device Success. • Exclusion changes: reduced Covid-19 diagnosis to 30 days and clarified planned major amputation is target limb. • Clarified treatment of non-target lesions in exclusion criteria and Section 7.7.3. • Clarified edit to Section 7.7 that allows treatment with the Mini S catheter if the distal portion of the target lesion is found to extend below the ankle joint. • Updated Figure 2 Mini S IVL Treatment Algorithm and added configuration may be chosen after first 20 subjects in section 7.7. • Defined Destination Therapy in Section 7.7.10. • Removed “Unlikely” from relatedness from Section 10.2. • Updated dissection classifications and added requirement to document all dissections as AEs. • General Edits	Clinical

D	07/21/2023	26303	• Section 2.0, Study Summary: Primary Safety Endpoint definition modification of the Major Adverse Events (MAE). Secondary Endpoints, addition of Technical Success (final), clarification of MAEs as composite and individual components, and administrative changes. • Section 2.0, Study Summary: Clarification of Angiographic Inclusion criteria #9 for tandem lesions, added "with the exception of toe amputation" to exclusion criteria #2, clarification of angiography exclusion criteria #18 (successfully treat inflow lesion), and administrative clarification of Angiographic Exclusion Criteria #19. • Section 4.1, Mini S Peripheral IVL Catheter: Clarified catheter shaft color. • Section 5.1, Safety Endpoints: Primary Safety Endpoint definition modification. Clarification of MAE reporting as a "composite and individual components" • Section 5.2, Performance Endpoints: Addition of Technical Success (final) endpoint. • Section 7.2.1, Inclusion Criteria: Clarification of Angiographic Inclusion criteria #9 for tandem lesions • Section 7.2.2, Exclusion Criteria: added "with the exception of toe amputation" to exclusion criteria #2, Clarification of Angiographic Exclusion Criteria #18 (successfully treat inflow lesion), and administrative clarification of Angiographic Exclusion criteria #19 • Section 7.4, Table 1, Schedule of Events and Evaluations: Months	Clinical

Revision	Release Date	DCO #	Reason(s) for Revision	Doc Owner
			spelt out; TLR clarified from vessel to limb. • Figure 2: Spelling error correction on "delivery". • Section 9.2.1, Primary Safety Endpoint: Modification of Primary Safety Endpoint definition for consistency, clarification of event adjudications, and MAE analysis. • Section 9.2.2, Primary Performance Endpoint: Clarification of Primary Performance Endpoint analysis. • Section 12.9, Data Management: Clarification of Data Management activities along with database name from [redacted]. • Section 15, Definitions and Abbreviations: Update of MAE definition and clarifications of Rutherford Classifications. • General Administrative Edits throughout.	