CLotTriever **OUT**comes **(CLOUT)** Registry

Device: ClotTriever® Thrombectomy System
Protocol Number: 18-001
Version: 9.0
August 12, 2020

Sponsor
Inari Medical
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USA

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PROTOCOL SIGNATURE PAGE

Investigator Name	Title
Site Name	Site Number

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

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

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

Investigator's Signature	Date

SYNOPSIS

Protocol Number	18-001
Study Title	ClotTriever Outcomes (CLOUT) Registry
Study Device	ClotTriever® Thrombectomy System
Regulatory Status	The ClotTriever Thrombectomy System was cleared in the US under 510(k) number K163549, February 16, 2017. The device is indicated for the non-surgical removal of soft thrombi and emboli from peripheral blood vessels.
Sponsor	Inari Medical 9 Parker, Suite 100 Irvine, CA 92618 (USA)
Primary Study Objective	The primary objective of this study is to evaluate real world patient outcomes after treatment of acute, subacute, and chronic proximal lower extremity deep venous thrombosis (DVT) with the ClotTriever Thrombectomy System.
Study Population	The Full Analysis dataset comprises up to 500 subjects with proximal lower extremity DVT. The Primary Analysis datasets are subsets of the Full Analysis dataset, comprising 91 subjects with unilateral acute or subacute DVT of less than or equal to 6 weeks' duration. • Primary Safety Cohort are subjects in the Primary Analysis dataset who were not treated with thrombolytic or percutaneous mechanical thrombectomy within the prior 3 months. • Primary Effectiveness Cohort are subjects in the Primary Analysis dataset with core laboratory-documented intraluminal thrombus at baseline who have at least one target venous segment (TVS) treated with the study device.
Number of Sites	The study will be conducted at up to 50 sites.
Study Design	The CLOUT Registry is a prospective, multi-center, observational study of subjects with proximal lower extremity DVT treated with the ClotTriever Thrombectomy System. The Registry will collect data on demographics, comorbidities, details from the DVT diagnosis and treatment, and clinical outcomes through 2-year follow-up.
Primary Endpoints (Primary Analysis Cohorts)	Primary Safety Endpoint: Composite of Major Adverse Events (MAEs) through 30 days defined as one or more of the following: • All-cause mortality • Major bleeding • New symptomatic PE documented by CTPA • Rethrombosis of a TVS Primary Effectiveness Endpoint: Technical Success defined as complete or near complete (≥75%) removal of venous thrombus from the TVS.

Secondary Endpoints (Primary Analysis Cohorts)	The following will be assessed as secondary endpoints of the study:
	• Individual components of the MAE composite endpoint through 30 days
	• Minor bleeding through 30 days
	• Access site complications from the index procedure (hematoma, false aneurysm, perforation) through 30 days
	• Device-related death
	• Procedure-related death
	• At any point during follow-up:
	  ○ TVS patency by duplex ultrasound
	  ○ Rethrombosis of the TVS
	  ○ Device-related rethrombosis of the TVS
	  ○ DVT outside of the TVS
	  ○ Target limb edema (edema scale of the rVCSS) compared to baseline
	  ○ Pain (NPRS) compared to baseline
	  ○ EQ-5D, rVCSS, Villalta scores compared to baseline (except discharge)

Inclusion Criteria	Subjects must meet the following criteria to be included in the study: 1. Age ≥ 18 years 2. Proximal lower extremity DVT involving the femoral, common femoral, iliac veins or inferior vena cava (IVC), alone or in combination 3. Willing and able to provide informed consent
Exclusion Criteria:	Subjects will be excluded from the study for: 1. Prior venous stent in a TVS 2. IVC aplasia/hypoplasia or other congenital anatomic anomalies of the IVC or iliac veins 3. IVC filter in place at the time of the index procedure 4. Allergy, hypersensitivity, or thrombocytopenia from heparin or iodinated contrast agents, except for mild to moderate contrast allergies for which pretreatment can be used 5. Life expectancy less than 1 year 6. Chronic non-ambulatory status 7. Known hypercoagulable states that, in the opinion of the Investigator, cannot be medically managed throughout the study period 8. Unavailability of a proximal lower extremity venous access site
Follow-Up Schedule	Subjects will have required follow-up evaluations after the index procedure at: discharge, 30 days, 6 months, 1 year, and 2 years.
Primary Analysis Sample Size Calculation	The sample size is driven by the primary safety endpoint. A performance goal of 34% has been established, based on a one-sided 97.5% exact binomial test. The 30-day MAE rate is anticipated to be approximately 20%. Under these assumptions, the required sample size to achieve a level of 82% power is 86 subjects. Assuming 5% attrition over 30 days, a sample size of 91 subjects is necessary.

Analytic Datasets	In total, up to 500 subjects may be enrolled in the Full Analysis dataset. The Primary Analysis dataset will comprise subjects with unilateral acute or subacute DVT of less than or equal to 6 weeks' duration, without recent (≤3 month) venous interventions. The first 91 subjects enrolled in the Primary Analysis dataset will comprise the Primary Analysis Safety cohort for safety assessment. Effectiveness will be evaluated in the primary analysis cohort with core lab adjudication of intraluminal thrombus.
Medical Monitor	An independent Medical Monitor will review adverse events and other important safety occurrences as specified in the Safety Plan.
National Principal Investigators	Robert Beasley, M.D. Mount Sinai Medical Center Miami Beach, FL David Dexter, M.D. Sentara Healthcare Norfolk, VA

Schedule of Assessments

Assessment	Baseline* (-7 to 0 days)	Index Procedure (day 0)	Discharge	30 Days (14 to 45 days)	6 Months (46 to 270 days)	1 Year (271 to 540 days)	2 Years (541 to 900 days)	Unscheduled Visits
Medical history	X							
Physical examination†	X		X	X	X	X	X	X
Inclusion/exclusion criteria	X							
Anticoagulation regimen	X	X	X	X	X	X	X	X
Duplex ultrasound§	X			X	X	X	X	X
Venogram (Required)		2x+						
IVUS (Expected)		2x+						
Access site examination			X	X				
Adverse event assessment		X	X	X	X	X	X	X
CEAP Score‖	X							
EQ-5D, Villalta, rVCSS Quality of Life Assessments	X			X	X	X	X	
Edema and Numeric Pain Rating Scale (NPRS) assessment	X		X	X	X	X	X	

*Baseline assessments must be performed no more than 7 days prior to the index procedure or after the onset of symptoms in those subjects with less than 7 days' symptom duration.

†Physical examination is limited to the involved lower extremity(ies). Examination will include an assessment of leg edema, graded as per the rVCSS scale; mild (limited to foot and ankle), moderate (above ankle but below knee), or severe (knee and above), and recorded on the right and left legs.

§Duplex ultrasound will include patency assessments of all target lesions including flow (present, absent, or not evaluable) and compressibility (normal, partial, incompressible, not evaluable).

+ Imaging will be captured before ClotTriever treatment and after ClotTriever treatment but before adjunctive therapy (if any). If adjunctive therapy is utilized, a third set of images will be obtained afterwards. In addition, if a reintervention is performed, the same imaging timing and transfer are required. Note that adjunctive therapy is defined as an additional thrombus removal strategy after ClotTriever thrombectomy has been completed (i.e. balloon, stenting, and placement of IVC filters during ClotTriever procedure session would NOT be considered adjunctive therapy).

‖CEAP (Clinical, Etiologic, Anatomic, and Pathophysiologic) score is a clinical classification score developed to allow uniform diagnosis and stratification of patient populations according to the severity of their presentation

ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ATTRACT	Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis
BMI	Body Mass Index, calculated as weight in kg divided by height in m squared
CDT	Catheter Directed Thrombolysis
CEAP	Clinical, Etiologic, Anatomic, Pathophysiologic
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CT	ClotTriever
CTPA	Computed Tomography Pulmonary Angiogram
DOAC	Direct Oral Anticoagulant
DVT	Deep Vein Thrombosis
FDA	US Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ICU	Intensive Care Unit
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
IVC	Inferior Vena Cava
IVUS	Intravascular Ultrasound
LOS	Length of Stay
MAE	Major Adverse Event in the ITT population
MLA	Minimum Lumen Area
MLD	Minimum Lumen Diameter
NPRS	Numerical Pain Rating Scale
PE	Pulmonary Embolism
PHI	Personal Health Information
PMT	Percutaneous Mechanical Thrombectomy
PP	Per Protocol
PTS	Post-Thrombotic Syndrome
RVA	Reference Vessel Area
RVD	Reference Vessel Diameter
rVCSS	Revised Venous Clinical Severity Score
TVS	Target Venous Segment(s)
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism

1 INTRODUCTION AND BACKGROUND

1.1 DEEP VEIN THROMBOSIS: DEFINITION, ANATOMY, AND PATHOPHYSIOLOGY

Deep vein thrombosis (DVT) develops when a blood clot (thrombus) forms in a deep vein.[1] Most DVT occur in the legs, but can also occur in the arms, as well as the mesenteric and pelvic veins.[2] Lower extremity DVT is classified as either proximal or distal.[3] Proximal DVT is defined when the process involves the iliac, deep femoral, or popliteal veins, whereas distal DVT occur in the veins of the calf, most frequently in the posterior tibial and peroneal veins, and less frequently in the anterior tibial and soleal/gastrocnemius veins.[3,4] Notably, the risk of subsequent embolization in proximal DVT is double that of isolated distal DVT.[3] Hence, proximal DVT have a less favorable prognosis.[5] Regardless of the vein in which it forms, DVT tend to originate on the venous endothelium in regions of sluggish blood flow above and below venous valves.[2,5]

The pathophysiology of DVT has been attributed to three principal risk factors: a change in blood flow in the form of venous stasis, endothelial injury, and blood hypercoagulability – known collectively as Virchow's triad.[6] Stasis sufficient to precipitate DVT can result from prolonged immobility, due to – for example – a long plane trip or train ride, or secondary to a paralytic neurological injury.[7] The significant role that venous stasis plays in the etiology of DVT is most clearly demonstrated by the finding that stroke patients with hemiparesis have a sevenfold greater risk of developing DVT in their paralyzed leg relative to their non-paralyzed leg.[6] Relevant causes of endothelial injury include trauma, recent surgery, and intravenous drug use.[7] Hypercoagulability can stem from inflammatory conditions such as systemic lupus erythematosus or inflammatory bowel disease, cancer, sepsis, previous thromboembolic disease, the nephrotic syndrome, or inherited or acquired thrombophilia.[7-10] Additional risk factors that do not fit neatly into Virchow's triad include pregnancy, oral contraceptive use, cardiac disease, age greater than 60 years, cytotoxic chemotherapy, and obesity.[7,9] Some risk factors are more consequential than others. For instance, paralytic neurological injury is significantly more dangerous than prolonged immobility.[9] Many DVT patients have multiple simultaneous risk factors. In one DVT patient cohort, 76% of patients with DVT had two or more risk factors, and 39% had three or more.[9] Moreover, these factors tend to be additive.[7,9] Beyond those cases in which at least one risk factor is clearly present, some DVT are idiopathic.[5]

Venous thrombi are made of a fibrin-bound aggregate of red blood cells, white blood cells, and platelets.[2] They form when tissue factor is exposed, thrombin is created, and fibrinogen is transformed into fibrin.[8] Once the clots have formed, they often resolve – as least to some degree – on their own. Among one group of DVT patients, 86% showed some degree of venous reopening (recanalization) within 3 months of the initial clotting event.[5] The smaller the size of the thrombi, the more quickly and completely recanalization occurs.[5] However, recanalization is not always the positive development one might suppose, since it is when clots begin to migrate away from the veins and back toward the heart that some of the most significant DVT sequelae can arise. When they embolize, clots can find their way into the pulmonary circulation, where they can cause a pulmonary embolism (PE). They also have the potential to enter the arterial circulation by way of an atrial septal defect, or a patent foramen ovale.[8]

1.2 COMPLICATIONS OF DVT

Some of the most important sequelae of DVT include PE, the post-thrombotic syndrome (PTS), and the formation of recurrent DVT. PE can lead to alveolar hyperventilation, diminished gas exchange, decreased pulmonary compliance, and increased airway resistance.[2,8] This cascading chain of physiological derangements can eventually cause right heart failure, ultimately leading to death in some cases.[8] In PTS, incomplete recanalization after a DVT clot causes venous obstruction, which in turn results in venous hypertension. In response to this hypertension, capillaries dilate and become more permeable, which can cause localized edema, leg pain, eczema, and venous ulceration.[11] One additional complication of DVT is called phlegmasia cerulea dolens (blue, painful leg) in which a

large DVT totally blocks arterial flow, yielding limb discoloration and ischemia, venous gangrene, and systemic hypovolemic shock.

DVT result in PE in 15 to 32% of cases, and PTS in 56% of cases.[12] Because it is so common for DVT and PE to present concurrently, they are sometimes considered to be part of a single disease entity: venous thromboembolism (VTE).[2] In addition, DVT has a recurrence rate – from time of initial diagnosis – of 10% at 1 year, 24% at 5 years, and 30% at 8 years.[5,12] The case fatality rate among hospitalized patients with DVT is 5%, and 5-year mortality can be as high as 39%.[5] Despite this, it is nonetheless important to bear in mind that in at least some cases, DVT does not result in any pathology whatsoever.[13]

1.3 MEDICAL AND ECONOMIC IMPACT OF DVT

In both human and economic terms, DVT and subsequent VTE exact substantial costs. In 2016, the worldwide incidence rate of VTE was 115 to 269 per 100,000, with a corresponding worldwide mortality rate of 9.4 to 32.3 per 100,000.[14] One study found that, in high-income countries in 2014, VTE necessitating hospitalization was the second leading cause of disability-adjusted-life-years lost, which exceeds those lost to adverse drug events and nosocomial pneumonia.[15] In Europe, VTE is estimated to kill 370,000 people every year – a total greater than that caused by AIDS, breast cancer, prostate cancer, and automobile accidents combined – and costs the continent roughly $3.7 billion annually.[8,9,16] In the United States, there are approximately 2 million annual cases of DVT, which result in about 250,000 hospitalizations and 300,000 deaths – more than those due to myocardial infarction or stroke.[5,7,8] Even more Americans are at risk for DVT. Since about one quarter of DVT is acquired in the hospital, close to 14 million hospitalized patients are at risk of acquiring it annually.[8] All of this costs between $9 billion and $52 billion a year.[17]

1.4 DVT TREATMENT AND CURRENT SHORTCOMINGS

The standard of care after an initial DVT episode consists of anticoagulant treatment for 3 months.[3,18,19] For patients who have had a second episode, or who have persisting hypercoagulable comorbidities such as malignancy, guidelines recommend extended anticoagulation (i.e., treatment without a scheduled stopping point).[18] Although there is widespread consensus that all proximal DVT should be treated with anticoagulation, there is some controversy over whether, and when, it is indicated for isolated distal DVT.[3,18-20]

Anticoagulation should only be initiated after DVT has been diagnosed, most commonly by duplex ultrasound of the legs.[3,5,21,22] Several different anticoagulants are used to treat DVT. Among these are various preparations of heparin – which works by boosting the suppression of factor Xa and thrombin by antithrombin – and vitamin K antagonists (VKAs) such as warfarin.[19,21,23] Newer agents called direct oral anticoagulants (DOACs), which inhibit either thrombin or factor Xa, are also available.[23] American Heart Association DVT treatment guidelines recommend 5 days initial anticoagulation with heparin, as well as concomitant and subsequent administration of a VKA, or a DOAC, for longer term anticoagulation.[19,23] The American College of Chest Physicians suggests initiating therapy with a DOAC rather than a VKA, with or without initial anticoagulation, depending on the specific agent used.[18]

Unfortunately, there are significant limitations associated with the use of anticoagulants as sole treatment after DVT. Most importantly, although anticoagulation therapy can help prevent new thrombi from forming, it is incapable of dissolving preexisting clots, regardless of which specific medication is employed.[5] Despite anticoagulation therapy, PTS manifests in approximately 50% of DVT patients within 2 years.[24,25] Limitations specific to VKAs include a narrow therapeutic index, the need for routine coagulation monitoring due to patients' genetic variability, which can result in pharmacokinetic and pharmacodynamic heterogeneity, and a large number of interactions with foods and other medications.[5,23,26] Bleeding events commonly occur in those on anticoagulants, the most devastating of which is intracranial bleeding. As well, many oral anticoagulants have

teratogenic effects, limiting use in pregnancy or during nursing.[21,23,27] DOACs, in turn, are contraindicated in patients with severe renal failure, and may increase the chance of gastrointestinal bleeding.[23] Also, DOACs pose unique therapeutic drug monitoring challenges.[23] And whereas VKAs can be reversed with vitamin K and prothrombin complex concentrate, only one out of the four DOACs currently approved in the United States is reversible.[23]

Beyond anticoagulants, other DVT treatment modalities are available. Elastic compression stockings – which reduce the frequency of PTS – can sometimes be helpful, and the American College of Chest Physicians advises that they should be used in most cases.[18,28] However, 21.1% of patients treated with stockings still go on to develop PTS.[28] Another treatment option is thrombolytic therapy, in which thrombolytic medications, such as tissue-type plasminogen activator, are administered intravenously, in the hope of lysing the clot, and thereby diminishing the risk of PE and PTS.[29] But difficulties associated with this approach include complications such as intracerebral hemorrhage.[30] It is also possible to treat DVT via pharmacomechanical thrombolysis, in which thrombolytic medication is applied directly into the clot, while the clot is simultaneously excised through mechanical means.[25] Nevertheless, recent evidence has demonstrated that, relative to standard anticoagulation alone, pharmaco-mechanical thrombolysis does not diminish the risk of PTS, even though it does heighten the chance of major hemorrhage.[19] For instance, the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) study randomized 692 patients with acute proximal DVT to receive either anticoagulants alone, or anticoagulants and pharmacomechanical thrombolysis. The study found that the two groups did not differ as to the proportion of patients who developed PTS, whereas the pharmacomechanical thrombolysis group had a greater number of major bleeding events within 10 days.[27]

1.5 RATIONALE FOR THE CLOTTRIEVER THROMBECTOMY SYSTEM

Considering the drawbacks of anticoagulation alone, elastic compression stockings, thrombolytic therapy, and pharmacomechanical thrombolysis, patients have the potential to benefit from a safer and more effective DVT treatment, which the Inari Medical ClotTriever Thrombectomy System has the potential to provide. The ClotTriever is a new treatment option that enables the extraction of extensive thrombi from large vessels without the need for thrombolytic medications. It is an over-the-wire system uniquely designed to capture and remove significant occluding venous thrombi.

2 STUDY DEVICE

2.1 OVERVIEW

The ClotTriever Thrombectomy System is a single-use over-the-wire catheter-based system. The device was cleared in the US under 510(k) number K163549, February 16, 2017. The device is indicated for the non-surgical removal of soft thrombi and emboli from peripheral blood vessels.

2.2 MANUFACTURER

Inari Medical
9 Parker, Suite 100
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2.3 INDICATIONS FOR USE

The ClotTriever Thrombectomy System is a single-use over-the-wire catheter-based system for the minimally invasive treatment of thromboemboli in the peripheral vasculature. It is indicated for the non-surgical removal of soft thrombi and emboli from blood vessels, and injection, infusion, and/or aspiration of contrast media and other fluids into or from a blood vessel.

2.4 DEVICE DESCRIPTION

The ClotTriever Thrombectomy System is comprised of two main components packaged separately: the ClotTriever Sheath (CT Sheath) and the ClotTriever Catheter (CT Catheter).

The CT Sheath provides percutaneous access for the CT Catheter to the treatment site and provides a conduit for removal of the CT Catheter and thrombus from the subject after treatment. Refer to the Instructions for Use for the device specifications and information.

3 PRIOR INVESTIGATIONS

The Sponsor, Inari Medical (Irvine, CA), developed the study device known as the ClotTriever Thrombectomy System. The ClotTriever Thrombectomy System was cleared for marketing on February 16, 2017 and has been used clinically since that time. Prior to the current study, the ClotTriever Thrombectomy System has not been evaluated in a formal clinical study. The current study will allow the Sponsor to collect patient outcome data on the ClotTriever Thrombectomy System.

4 STUDY OBJECTIVES

The primary objective of this study is to evaluate real world patient outcomes after treatment of acute, subacute, and chronic proximal lower extremity DVT with the ClotTriever Thrombectomy System.

Secondary objectives will consist of the following:

- Assessment of post-thrombotic syndrome, as defined by the Villalta scale[31]
- Assessment of symptomatic improvement using the change in venous quality of life indices
- Determination of patency (primary, assisted primary, and secondary)
- Differences in outcome in the acute (≤14 days), subacute (>14 days ≤6 weeks), and chronic (>6 weeks) cohorts and in other subsets (see Section 10)

5 OUTCOME VARIABLES

5.1 PRIMARY SAFETY ENDPOINT DEFINITION

The primary safety endpoint is the rate of Major Adverse Events (MAE). MAEs are defined as a composite endpoint triggered when any of four categories of events through 30 days after the index procedure, as observed in the Primary Analysis Safety Cohort:

- All-cause mortality
- Major bleeding
- New symptomatic PE documented by CTPA
- Rethrombosis of a target venous segment (TVS)

The components of the composite MAE endpoint will be assessed by the independent Medical Monitor.

5.2 PRIMARY EFFECTIVENESS ENDPOINT DEFINITION

The primary effectiveness endpoint is Technical Success, as measured in the Primary Analysis Effectiveness Cohort. Technical Success is defined as complete or near complete (≥75%) removal of venous thrombus from the TVS. The endpoint will be determined volumetrically by the percent reduction in the Marder score from baseline (pre-intervention) venogram to the venogram performed ***after*** use of the study device but ***before*** the use of other adjunctive treatment modalities such as pharmacologic thrombolysis, other mechanical thrombectomy devices, or other intervention with pharmacologic or mechanical means. Adjunctive therapy is defined as an additional thrombus removal strategy after ClotTriever thrombectomy has been completed (i.e. balloon, stenting, and placement of IVC filters during ClotTriever procedure session would NOT be considered adjunctive therapy).

5.3 SECONDARY ENDPOINTS

The following secondary endpoints will be studied in the Primary Analysis Cohorts:

- Individual components of the MAE composite endpoint through 30 days
- Minor bleeding through 30 days
- Access site complications from the index procedure (hematoma, false aneurysm, perforation) through 30 days
- Device-related death
- Procedure-related death
- At any point during follow-up:
  - TVS patency by duplex ultrasound
  - Rethrombosis of the TVS
  - Device-related rethrombosis of the TVS
  - DVT outside of the TVS
  - Target limb edema (edema scale of the rVCSS) compared to baseline
  - Pain (NPRS) compared to baseline
  - EQ-5D, rVCSS, Villalta scores compared to baseline (except discharge)

6 STUDY DESIGN

The CLOUT Registry is a prospective, multi-center, observational study of subjects with proximal lower extremity DVT treated with the ClotTriever Thrombectomy System. The Registry will collect data on demographics, comorbidities, details from the DVT diagnosis and treatment, and clinical outcomes through 2-year follow-up.

Up to 500 subjects with proximal lower extremity DVT will be enrolled at up to 50 Registry sites. All subjects who sign consent and are treated with the ClotTriever System will comprise the Full Analysis dataset.

The Primary Analysis datasets will be derived from the 500 subject Full Analysis dataset. Hypothesis testing will be performed on this dataset; the safety endpoint testing will be performed on the Primary Analysis Safety cohort and the effectiveness endpoint testing will be performed on the Primary Analysis Effectiveness Cohort.

- The Primary Analysis Safety cohort will include the first 91 subjects that enroll with a clinical presentation analogous to that used for the literature-derived performance goal (i.e., unilateral acute or subacute DVT of less or equal to 6 weeks' duration). These first 91 subjects will not have been not treated with thrombolytic or percutaneous mechanical thrombectomy within the prior 3 months.
- From these same 91 subjects, the Primary Analysis Effectiveness cohort will be the subset of subjects who undergo treatment with the ClotTriever System in venous segments with Core Laboratory determined intraluminal thrombus.

Once the Primary Analysis cohort is fully accrued, subjects meeting these criteria will continue to be enrolled and will be evaluated as part of the Full Analysis dataset.

The primary safety endpoint will be assessed when the 30-day follow-up data on the 91-subject Primary Analysis cohort is complete (see Section 10.4), allowing evaluation of both the primary safety and effectiveness endpoints. The remainder of the subjects will be enrolled to obtain additional safety and effectiveness data and to allow subset analyses of various pre-determined subgroups. Subjects in both arms will be followed for 2 years after the index procedure.

6.1 STUDY POPULATIONS

The study will consist of up to 500 subjects, i.e., the Full Analysis dataset, who meet the eligibility criteria and are appropriate candidates for treatment with the ClotTriever Thrombectomy System. The Primary Analysis dataset is a subset of subjects with unilateral acute or subacute DVT of less or equal to 6 weeks' duration, without recent (≤3 months) venous intervention. The first 91 subjects enrolled who meet these criteria will complete the Primary Analysis dataset. Enrollment of this type of subject will continue once the Primary Analysis cohort is fully accrued, i.e., past the 91 subjects needed for the primary endpoint analyses. These additional subjects will be included in the Full Analysis dataset.

6.2 INFORMED CONSENT

Written, study-specific Informed Consent will be obtained from each subject prior to the subject's deidentified medical record or personal health information (PHI) being shared with any study representative. The Investigator will keep the original Informed Consent Form and a copy will be given to the subject. The subjects will be informed that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. See Section 7.2 for additional information regarding the timing of consent and the point of enrollment.

6.3 POINT OF ENROLLMENT

The ClotTriever System is not being used in an investigational manner and the patient will be treated with the device in the same manner regardless of whether the patient enrolls in the study. Therefore, the patient's consent for treatment is covered under the institution's internal procedures. To participate in the study, the patient must consent to share his/her deidentified personal health information (PHI) with the study sponsor. This allows sites to treat patients prospectively and consent patients after treatment. This can be helpful for sites when the research staff is unavailable to consent the patient prior to the index procedure (i.e., after hours, weekends, holidays). This practice is allowed provided there is no institutional prohibition against post-procedure consent.

Pre-procedure consents are the preferred consenting method and should be obtained ***within*** 7 days of the scheduled index procedure as part of the baseline work-up. When post-procedure consents are obtained, the consent must be obtained ***after*** the patient gains full capacity after anesthesia ***and within*** 7 days of the index procedure.

If the ClotTriever System does not enter the patient's vasculature, the patient is considered a screen failure and as such, his/her data is not to be entered into the database. A patient is considered enrolled when 1) the device enters the patient and 2) the patient consents to the study. The timing of the two events, index procedure and consent, are interchangeable.

6.4 INCLUSION CRITERIA

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

6.4.1 Age ≥ 18 years

6.4.2 Proximal lower extremity DVT involving the femoral, common femoral, iliac veins or inferior vena cava (IVC), alone or in combination[a]

6.4.3 Willing and able to provide informed consent

6.5 EXCLUSION CRITERIA

Subjects will be excluded from the study for any of the following:

6.5.1 Prior venous stent in a TVS

6.5.2 IVC aplasia/hypoplasia or other congenital anatomic anomalies of the IVC or iliac veins

6.5.3 IVC filter in place when ClotTriever system enters the patient (Patients can be included if an existing IVC filer is removed prior to insertion of the ClotTriever system)

6.5.4 Allergy, hypersensitivity, or thrombocytopenia from heparin or iodinated contrast agents, except for mild to moderate contrast allergies for which pretreatment can be used

6.5.5 Life expectancy less than 1 year

6.5.6 Chronic non-ambulatory status

6.5.7 Known hypercoagulable states that, in the opinion of the Investigator, cannot be medically-managed throughout the study period

[a] Subjects with bilateral DVT may be enrolled but will not be included in the Primary Analysis Dataset.

6.5.8 Unavailability of a proximal lower extremity venous access site[b]

7 ASSESSMENTS AND FOLLOW-UP SCHEDULE

7.1 SCHEDULE OF ASSESSMENTS

The data collected will be standard-of-care. In this regard, the Schedule of Assessments comprises recommended evaluations, and any departures from the schedule will not be considered Protocol Deviations (see Section 11.3).

Table 1. Schedule of Assessments

Assessment	Baseline* (-7 to 0 days)	Index Procedure (day 0)	Discharge	30 Days (14 to 45 days)	6 Months (46 to 270 days)	1 Year (271 to 540 days)	2 Years (541 to 900 days)	Unscheduled Visits
Medical history	X							
Physical examination†	X		X	X	X	X	X	X
Inclusion/exclusion criteria	X							
Anticoagulation regimen	X	X	X	X	X	X	X	X
Duplex ultrasound§	X			X	X	X	X	X
Venogram (Required)		2x+						
IVUS (Expected)		2x+						
Access site examination			X	X				
Adverse event assessment		X	X	X	X	X	X	X
CEAP Score‖	X							
EQ-5D, Villalta, rVCSS Quality of Life Assessments	X			X	X	X	X	
Edema and Numeric Pain Rating Scale (NPRS) assessment	X		X	X	X	X	X	

*Baseline assessments must be performed no more than 7 days prior to the index procedure or after the onset of symptoms in those subjects with less than 7 days' symptom duration.

†Physical examination is limited to the involved lower extremity(ies). Examination will include an assessment of leg edema, graded as per the rVCSS scale; mild (limited to foot and ankle), moderate (above ankle but below knee), or severe (knee and above), and recorded on the right and left legs.

§Duplex ultrasound will include patency assessments of all target lesions including flow (present, absent, or not evaluable) and compressibility (normal, partial, incompressible, not evaluable).

+ Imaging will be captured before ClotTriever treatment and after ClotTriever treatment but before adjunctive therapy (if any). If adjunctive therapy is utilized, a third set of images will be obtained afterwards. In addition, if a reintervention is performed, the same imaging timing and transfer are required. Note that adjunctive therapy is defined as an additional thrombus removal strategy after ClotTriever thrombectomy has been completed (i.e. balloon, stenting, and placement of IVC filters during ClotTriever procedure session would NOT be considered adjunctive therapy).

‖CEAP (Clinical, Etiologic, Anatomic, and Pathophysiologic) score is a clinical classification score developed to allow uniform diagnosis and stratification of patient populations according to the severity of their presentation

[b] For example, from a popliteal, femoral or other infrainguinal vein on either side. Jugular access is not allowed.

7.2 BASELINE ASSESSMENT

The Baseline Assessment includes diagnostic testing, patient status, and eligibility verification for study participation including:

- Review inclusion/exclusion to ensure patient meets criteria
- Review duration of symptoms
- Confirm venous thrombus presence on duplex ultrasound

If the patient meets all eligibility criteria and is scheduled for the thrombectomy procedure, the patient may be invited to participate in the study.

The data captured for the Baseline Visit may be gathered over the course of more than one office visit; however, the data must have been obtained ***within*** 7 days of the scheduled index procedure date ***and***, for subjects with symptoms of less than 7 days' duration, ***after*** the onset of symptoms.

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

- Demographic information
- Medical history including risk factors
- Physical examination including an edema evaluation of both legs[c]
- Presence of relative and absolute contradictions to pharmacologic thrombolysis
- Anticoagulation Regimen
- Duplex ultrasound assessment of patency of the TVS
- CEAP Score
- EQ-5D, Villalta, rVCSS,
- Edema and Numeric Pain Rating Scale (NPRS)

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

Subjects with bilateral DVT may be enrolled. Each leg's TVS will be counted separately in the 500-subject Full Analysis dataset. The second leg may only be enrolled and treated at the time of the primary leg's index procedure.

[c] Measurements are to be taken from three locations: (1) Thigh = midpoint between the hip and the proximal edge of the patella; (2) Mid-Calf = midpoint between the tibial tuberosity and the medial malleolus; and (3) Ankle = 2 cm about the medial malleolus.

7.3 INDEX PROCEDURE

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

Anticoagulation therapy to ensure an activated clotting time of 250 – 300 seconds is recommended.

Subjects who require conversion to open surgery due to treatment failure with the device will be followed for safety through 30 days, or until any treatment related adverse events resolve, which ever is later.

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

- Length of procedure (from ClotTriever sheath access to last removal of sheath)
- Number of ClotTriever passes
- Number of ClotTriever devices used, with lot numbers
- Largest sheath size used
- Pre- and post-procedure venogram findings
- Pre- and post-procedure IVUS measurements
- Concurrent use of balloon angioplasty and/or stenting and/or placement of IVC Filter
- Adjunctive therapy (thrombolysis and/or additional thrombectomy).
- Anticoagulant used and amount

Venogram runs/cines must be, and IVUS runs should be, acquired pre-ClotTriever and post-ClotTriever[d]. If adjunctive therapy is used, a third venogram and IVUS run post-therapy will be acquired. All procedural venograms cines and IVUS images will be de-identified, labeled appropriately, uploaded and sent to the Core Laboratory.

7.4 TARGET VESSEL SEGMENT (TVS) ASSIGNMENT

The target vessel segment (TVS) is thrombus-containing venous segments, specified by the operator, that were treated with the study device at the index procedure. These segments may include the popliteal vein, caudal femoral vein, cranial femoral vein, profunda/deep femoral vein, common
femoral vein, external iliac vein, internal iliac vein, common iliac vein, or the inferior vena cava. The TVS does not include segments that were not intentionally treated but were instead passed through to remove the device from the leg.

All vessels treated in one leg/side are recorded under one TVS. There are three possible TVS designations:

- For unilateral treatment: TVS 1 = Leg 1 and can be any or all segments from the IVC to the popliteal
- For bilateral treatment *only*: TVS 2 = Leg 2 and will not include the IVC (if the IVC was treated, record it as part of TVS 1)
- For IVC treatment *only*: Neither leg was treated, and the treatment was IVC only (designate as TVS 1)

d Ballooning and/or stenting and/or IVC placement during the procedure is routine and not considered adjunctive therapy. Adjunctive therapy includes thrombolysis and additional thrombectomy.

7.5 CLINIC/HOSPITAL DISCHARGE ASSESSMENT

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

- Time spent in ICU and hospital
- Physical examination of the target proximal lower extremity(ies), including an edema evaluation of both legs
- Anticoagulation regimen
- Examination of access site for wound complications
- Rethrombosis since leaving the procedure room
- Reintervention since leaving the procedure room
- AE observations
- Blood transfusions
- Edema and Numeric Pain Rating Scale (NPRS)

Thrombus removal interventions that are performed at the end of the index procedure prior to the subject leaving the procedure room will be reported as adjunctive procedures and are not tabulated as reinterventions. In addition, before the subject has left the procedure room, formation of thrombus within the treated TVS is not reported as a rethrombosis when it occurs during the index procedure.

7.6 FOLLOW-UP ASSESSMENTS AND WINDOWS

Follow-up evaluation will be scheduled at 30 days (14-45 days), 6 months (46-270 days), 1 year (271-540 days), and 2 years (541-900 days) post-procedure. The following assessments and procedures will be performed at each follow-up visit:

- Physical examination of the target proximal lower extremity(ies), including an edema evaluation of both legs
- Anticoagulation regimen
- Duplex ultrasound of TVS for patency[e]
- Rethrombosis since the last visit
- Reinterventions since the last visit
- AE observations that occurred since the last visit
- Quality of life indices (EQ-5D, Villalta, and rVCSS)
- Edema and Numeric Pain Rating Scale (NPRS)

7.7 PROCEDURES, REINTERVENTIONS, AND RETHROMBOSIS

After the index procedure, conditions warranting additional treatment may present. Any intervention taken to treat a condition involving the initially treated TVS shall be documented. Adjunctive therapy is defined as an

[e] Duplex ultrasound will also be performed at unscheduled visits when the reason for the visit was potentially a patency-related event. The duplex ultrasound examination will specify whether each TVS was a) normal (compressible with flow), b) abnormal but patent (partially compressible with flow), or c) occluded (absent flow or incompressible). In the presence of a double femoral vein and when only one of the veins was treated, the sonographer must be certain to perform the duplex ultrasound assessment on the treated vein.

additional thrombus removal strategy after ClotTriever thrombectomy has been completed (i.e. balloon, stenting, and placement of IVC filters during ClotTriever procedure session would NOT be considered adjunctive therapy).

If a subject requires TVS venography during the follow-up period, the images must be sent to the core laboratory for analysis. For any TVS reintervention, pre- and post-reintervention images must also be sent.

7.8 UNSCHEDULED FOLLOW-UP VISITS

This Registry study was designed to capture real-world data regarding the clinical use of the ClotTriever Thrombectomy System. Therefore, the study will only record subject visits during the follow-up period that are related to the subject's DVT condition and treatment. If a subject returns to the site between scheduled follow-up visits for matters related to the study, the visit will be treated as an unscheduled visit and the assessments completed at this visit will be done at the discretion of the Investigator. CRF pages are provided for unscheduled visits and contain the same information as all the follow-up visits, in addition to the reason for the visit.

7.9 WITHDRAWALS AND LOST TO FOLLOW-UP

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

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

If the procedure is aborted, the subject does not need to complete the follow-up assessments, unless the subject is converted to surgical repair. Subjects who require conversion to open surgery due to treatment failure with the device will be followed for safety through 30 days, or until any treatment related adverse events resolve, which ever is later. The subject's enrollment roster position may not be made available to other subjects (i.e., the subject will not be replaced).

All efforts will be made to return subjects for all the follow-up visits. Due diligence in reaching the subject must be made by two documented telephone contact attempts, emails, or regular postal mail letters. After the above attempts are made, if no response is obtained, the final evaluation of the subject will be the last visit at which study-related procedures were performed. The End of Study/Study Exit CRF page will be completed, and communication attempts will be documented.

7.10 COVID-19 EFFECT ON RESEARCH

This Registry study was designed to capture real-world data regarding the clinical use of the ClotTriever System. As a result of the COVID-19 pandemic, clinic practice patterns may have been affected and patient visits may have been postponed or eliminated. In addition, some data may be collected from patients over the phone. Our goal is to collect as much real-world data as possible while protecting everyone's safety. In light of this situation, any deviation from the protocol due to COVID-19 will not be recorded as a protocol deviation (see Section 11.3 for additional information regarding protocol deviations).

8 RISK ANALYSIS

8.1 RISKS TO THE SUBJECTS

The CLOUT Registry involves the use and disclosure of deidentified personal health information. It collects only information relevant to the subject's DVT condition and its treatment.

The Registry study involves the collection of specific information for research and educational purposes only. It does not specify how the ClotTriever Thrombectomy System will be used to treat thrombus, and decisions regarding a subject's treatment are not influenced by the Registry study. Physicians participating in the Registry study are expected to review the indications, contraindications, warnings, precautions, and AEs described in the IFU. As with any endovascular procedure, the treating physician is expected to counsel the subject on the risks and benefits specific to the planned treatment and to obtain procedure-related informed consent per institutional policy and procedure.

8.2 RISK MITIGATION

This Registry study was designed to capture real-world data regarding the clinical use of the ClotTriever Thrombectomy System. The risk of providing this personal health information is believed to be minimal, as information directly identifying the subject will not be collected for the Registry database. All data handling will be in accordance with HIPAA requirements and only deidentified PHI will be used.

9 SAFETY ASSESSMENTS

9.1 DEFINING ADVERSE EVENTS

An AE is an untoward medical occurrence or exacerbation of an existing medical condition subsequent to treatment with the ClotTriever. AEs are classified in several ways, including severity, relationship, and seriousness.

- Severity (mild, moderate, severe)
  - ***Mild*****:** No limitation of usual activities, no therapy or only symptomatic therapy required to treat the injury or illness.
  - ***Moderate*****:** Some limitation of usual activities or specific therapy is required.
  - ***Severe*****:** Inability to carry out usual activities, hospitalization, emergency treatment, life threatening events, or death.
- Relationships (unrelated, device-related, procedure-related, or relationship unknown)
  - ***Unrelated:*** The clinical event is completely independent of study procedure/study device and/or evidence exists that the event is definitely related to another etiology.
  - ***Device-related:*** An event that can be directly attributed to the use of the device, wherein, if the device functioned 100% to specifications and expectations, the event would not have occurred.

  - Rethrombosis in the absence of device induced vascular trauma (documented on an imaging study or with direct visualization of the vessel) is not device-related; rather it is a complication related to ineffective anticoagulation therapy.
  - Perforation from the study device is device-related, but perforation from a non-study adjunctive device is not.
  - As well, events that occur as a result of downstream venous compression (e.g., May-Thurner syndrome) are not considered device-related.
- ***Procedure-related:*** An event that is not device-related and occurs as a result of the procedure.
  - Events that occur ≤30 days of the index procedure or ≤30 days of a secondary procedure performed for a previous procedure-related complication, if the event is not device-related.
  - Examples include complications from ineffective anticoagulation (e.g. rethrombosis), excessive anticoagulation (e.g. bleeding), or vascular access with a non-study device (e.g. generic sheath, guidewire injury); distant complications (e.g. myocardial infarction, pneumonia); or contrast-induced complications (e.g. contrast-induced nephropathy or hypersensitivity reaction).
- ***Relationship unknown*****:** The relationship to the study procedure/study device is not known.

- Seriousness (serious, non-serious)
  - ***Serious AE (SAE)*****:** An event that meets at least one of the following:

    Is fatal or life-threateningResults in persistent or significant disability/incapacityResults in permanent impairment of a body function or permanent damage to a body structure

    Results in hospitalization or prolongs a hospitalization and necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

9.2 REPORTING ADVERSE EVENTS

The CLOUT Registry study was designed to capture real-world data regarding the clinical use of the ClotTriever System and involves the collection of specific information for research and educational purposes only. It does not specify how the ClotTriever Thrombectomy System will be used to treat DVT, and decisions regarding a subject's treatment are not influenced by the study. This is a data collection study only; there is nothing investigational or experimental in the subject's medical treatment.

Therefore, the study will only capture AEs related to the subject's DVT condition and its treatment. Reportable AEs include all events considered in the safety analyses (i.e., major or minor bleeding, access site complications, new symptomatic PE within 30 days, or rethrombosis), all device- and/or procedure-related AEs, as well as any event resulting in death.

The AEs will be captured on the Adverse Event CRF and should include, wherever possible, severity, duration, outcome, and the Investigator's description of the event and his/her medical judgment as to the relationship of the AE (i.e., not related, related, or relationship unknown) to the study device, the index procedure or any subsequent procedure(s), to a thrombolytic agent or anticoagulant, or to underlying disease.

- Non-serious reportable AEs are to be submitted via the electronic data capture system (EDC) in a timely fashion.
- Reportable SAEs must be reported to the Sponsor within 5 business days of the Investigator's knowledge of the event. The event is reported in the electronic data capture system.

Appendix 1 includes a list of possible SAEs associated with thrombectomy, including those events considered major device-related events and major morbidity. These events are considered reportable at all time points throughout the study and require submission to the Sponsor.

10 STATISTICS AND DATA ANALYSIS

10.1 STATISTICAL METHODOLOGY

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

The safety and effectiveness performance goals were determined from a literature review of publications on the treatment of DVT. A total of seven studies were included in this review and, among these, all publications reported data referable to the primary safety endpoint and six of the seven publications reported data referable to the primary effectiveness endpoint. Studies with populations that overlapped the population of another study were excluded. In general, these studies report data on acute and subacute DVT, but not chronic.

10.2 PRIMARY SAFETY ENDPOINT ANALYSIS

The primary safety endpoint for this study will be assessed in the Primary Analysis Safety cohort and is a composite endpoint of any MAE within 30 days, as determined by the independent Medical Monitor. The MAE is defined as the 30-day rate of all-cause mortality, major bleeding, new symptomatic PE documented by CTPA, or rethrombosis of the target venous segment(s). The rate of MAE will be compared to a performance goal with the following null and alternative hypotheses:

H_0: $P_S \geq PG_S$ versus H_A: $P_S < PG_S$

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

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

10.3 PRIMARY EFFECTIVENESS ENDPOINT ANALYSIS

The primary effectiveness endpoint is Technical Success, defined by complete or near complete thrombus removal. Thrombus removal is determined by the Marder score at the index procedure, measured after use of the study device but prior to the use of adjunctive devices. Effectiveness will be assessed in the Primary Analysis Effectiveness Cohort[f] and will be compared to a performance goal with the following null and alternative hypotheses:

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

where P_E is the proportion of subjects with Technical Success, as defined complete or near complete removal of thrombus with the study device, defined by venographically-determined reduction of ≥75% in the Marder score in

f This dataset was designed to exclude those subjects treated who underwent venous thrombectomy for lesions that were non-thrombotic in nature. For instance, those with non-thrombotic May-Thurner lesions that have external compression or scar but who do not have demonstrable intraluminal thrombus. These subjects will remain in the Primary Safety Cohort and will be assessed for safety endpoints but will not be assessed for the effectiveness endpoints.

the TVSs. The effectiveness performance goal, PG_E, is Technical Success defined in the same manner, derived from the published literature.

10.4 Study Success Criteria

The study will be considered a success if both primary endpoints meet their respective performance goals. For the safety endpoint, this translates into observing a one-sided 97.5% lower confidence limit (LCL) of the point estimate below 34% and for the effectiveness endpoint, it means observing a one-sided 97.5% LCL above 30%.

10.5 Missing Data

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

10.6 Safety Performance Goal Derivation

The primary safety endpoint of 30-day MAE was assessed from published studies that treated DVT with pharmacologic means or with other thrombectomy devices. The weighted average MAE rate was 23.8%. Using a 10% margin and rounding to the nearest percent, the performance goal for the primary safety endpoint, 30-day freedom from MAE, was 34%. A detailed analysis of the safety performance goal will be described in the statistical analysis plan.

10.7 Effectiveness Performance Goal Derivation

The primary effectiveness endpoint of Technical Success was assessed from published studies that treated DVT with pharmacologic means or with other thrombectomy devices). The weighted average Technical Success rate was 39.3%. Using a 10% margin and rounding to the next percent, the performance goal for the primary effectiveness endpoint of Technical Success was 30%. A detailed analysis of the effectiveness performance goal will be described in the statistical analysis plan.

10.8 Sample Size

The performance goal of 34% has been established for the primary safety endpoint, based on a one-sided 97.5% exact binomial test. The 30-day MAE rate is anticipated to be approximately 20%. Under this assumption, the required sample size to achieve a level of 82% power is 86 subjects (**Table 2**). Assuming 5% attrition over 30 days, enrollment of 91 subjects is necessary for the Primary Analytic Dataset.

Table 2. Sample Size - Primary Safety Endpoint

Measure	
Performance goal	34%
Anticipated freedom from MAE	20%
Significance level	.025
Statistical test	One-sided exact binomial test
Desired power level	82%

Required sample size prior to 5% 30-day attrition rate	86
Required sample size after attrition adjustment	91

A performance goal of 30% has been established for the primary effectiveness endpoint. Anticipating an actual Technical Success rate of approximately 50%, and based upon a one-sided 97.5% exact binominal test, the required sample size to achieve a level of 97% power is 85 subjects (**Table 3**). Since the primary effectiveness endpoint is determined at the time of the index procedure, no attrition has been considered for lost to follow-up or other censoring events. However, the effectiveness endpoint is evaluated in the Primary Analytic Effectiveness cohort, and it is assumed that 3% of enrolled subjects will be treated for DVT in the absence of core laboratory-assessed visible thrombus in the TVS. Assuming a 3% attrition rate for subjects without thrombus, enrollment of 88 subjects will be necessary.

Table 3. Sample Size - Primary Effectiveness Endpoint

Measure	
Performance goal	30%
Anticipated technical success rate	50%
Significance level	.025
Statistical test	One-sided exact binomial test
Desired power level	97%
Required sample size prior to 3% attrition for subjects without thrombus	85
Required sample size after attrition adjustment	88

The required sample size is greater for the primary safety endpoint; 91 vs. 88 subjects. Thus, a total of 91 subjects will be enrolled in the Primary Analysis dataset; providing approximately 91 subjects in the Primary Safety cohort and 88 subjects in the Primary Effectiveness cohort for the primary safety and effectiveness analyses, respectively. The overall power of the study is 80%.

10.9 CONTINUED ENROLLMENT BEYOND THE PRIMARY ANALYSIS DATASET

Once the required number of subjects for the Primary Analysis dataset are enrolled, subject enrollment will continue in the Full Analysis dataset. In total, 500 subjects will be enrolled in the study, with a subset of 91 subjects in the Primary Analysis Dataset. The aggregate Full Analysis dataset will comprise the 91 Primary Analysis cohort and the 409 subjects not in that cohort. Enrollment of the 500 subject aggregate Full Analysis population will allow descriptive safety and effectiveness analyses on a larger dataset than would the Primary Analysis dataset alone, with subgroup analyses as described in Section 10.11.

Subjects who do not fit the criteria for the Primary Analysis Dataset will be enrolled in the Full Analysis Cohort in parallel (see Section 6.4). It is likely that the Primary Analysis Cohort will be enrolled before 409 subjects have been enrolled in the Full Analysis Cohort. Once enrollment in the Primary Analysis Cohort is fully accrued, subjects that subjects that would have met the criteria for inclusion into this subset will continue to be enrolled as part of the Full Analysis dataset.

10.10 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

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

10.11 SUBGROUP AND OTHER ANALYSES

The following subgroups will be analyzed:

- Acute (≤14 days) versus subacute (>14 days ≤6 weeks) versus chronic (>6 weeks)
- Iliofemoral versus femoropopliteal
- Men versus women
- Old versus younger (≥65 years, <65 years)
- Obese versus not obese (BMI ≥30 kg/m^2, >30 kg/m^2)

10.12 DATA POOLABILITY ASSESSMENT

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

The above statistical analyses do not result in an impediment to pooling, but rather assess the balance of baseline covariates across study sites. If any baseline covariate is found to be statistically significant by this process, generalized linear mixed model (GLMM) will be used to assess site heterogeneity. This is done by using site a random effect and further quantifying the heterogeneity in terms of Higgin & Thompson's I^2 index.

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

Baseline characteristics to be considered as possible covariates will include:

- Age
- Sex
- Coronary artery disease
- Chronic obstructive pulmonary disease
- Myocardial infarction
- Hyperlipidemia
- Cerebrovascular accident
- Hypertension
- Diabetes
- History of tobacco use
- Duration of symptoms
- Isolated iliofemoral DVT versus iliofemoral and distal DVT
- History of hypercoagulable state

- Obesity

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

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

11 STUDY MANAGEMENT CONSIDERATIONS

11.1 DATA MANAGEMENT: CLINICAL DATA

The Sponsor and/or designee will be responsible for the processing and quality control of the data. All source data, CRFs, copies of protocols and protocol amendments, correspondence, subject identification lists, informed consent forms, and other essential documents must also be retained for a period of at least 2 years after study completion or closure.

No study document or image will be destroyed without prior written agreement between the Sponsor and the Investigator prior to conclusion of the retention period (see Section 12.4.2). Should the Investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to the Sponsor.

11.2 PROTOCOL MODIFICATIONS

No changes from the final approved protocol will be initiated without the IRB's prior written approval of the amendment. The Principal Investigator will acknowledge an amendment by signing the Protocol Signature Page.

11.3 PROTOCOL DEVIATIONS

A protocol deviation is the non-adherence to or divergence from the protocol-specific required study procedures. For example, violations of the inclusion and exclusion criteria, improper or lack of consent, and lack of IRB approval, would all be considered protocol deviations.[g]

Given that this is a registry study capturing real-world data and standard of care may differ amongst sites, deviations from the protocol with regards to specific procedures, testing, and data points collected, as well as visit windows, will not be captured as a protocol deviation. However, the Sponsor will address any trends in omissions and deviations observed and work with the investigational site to improve data collection where possible.

[g] Subject eligibility for the study is determined by site-measured anatomic criteria, not by core laboratory values. For this reason, core laboratory-determined anatomic measurements from the baseline, pre-interventional angiogram are not part of subject eligibility determination and are not considered protocol deviations.

A record of reportable protocol deviations, as described above, will be maintained, and reviewed throughout the conduct of the study. The Sponsor will address deviations and take appropriate corresponding action. Continued non-compliance with the study protocol may lead to termination of the Investigator's participation in the study.

11.4 INFORMATION TO STUDY PERSONNEL

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

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

12 STUDY ADMINISTRATION

12.1 SITE INITIATION

A Site Initiation Visit (SIV) will be conducted by the Sponsor or designee in-person or via teleconference to ensure proper training of the Investigator and study staff members regarding the study protocol and data collection, as well as to ensure regulatory requirements are fulfilled prior to enrollment of the first study subject at a site.

12.2 STUDY MONITORING

Interim monitoring visits may be conducted by the Sponsor or designee in-person or remotely to ensure compliance with the protocol, and other written instructions and regulatory guidelines according to the study-specific monitoring plan.

The main responsibilities of the Monitor are to ensure adherence to the protocol; to verify all data are correctly and completely recorded and reported; and confirm that informed consent is obtained and recorded for each subject before any medical record or personal health information is shared with any study representatives. The Investigator and assisting staff must agree to cooperate with the Monitor or Sponsor representative to resolve any study-related problems, errors, or possible misunderstandings concerning the findings detected during these monitoring visits or data review.

12.3 STUDY TERMINATION

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

- Increased incidence of adverse experiences and/or the severity of such, suggestive of a potential, device-related health hazard
- Insufficient subject enrollment
- Recurrent protocol non-compliance, violations, or deviations

- Inaccurate, incomplete, and/or untimely data recording or query responses (>5 business days) on a recurrent basis
- Lack of cooperation with monitoring visits (e.g., failure to adequately prepare for visits, address action items from one visit to the next, or provide access to medical records)

12.4 DATA HANDLING AND RECORDKEEPING

12.4.1 Completing, Signing and Archiving Case Report Forms

Clinical study data will be collected using electronic case report forms (eCRFs). A web-based electronic data capture (EDC) database will be used to record and manage study data. eCRF completion guidelines, the instructions for electronic data-entry will be developed in conjunction with the Sponsor and/or the EDC vendor. All eCRFs must be kept in good order and updated so they always reflect the latest observations on the subjects participating in the study.

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

Because it is important to have proper data collection in a timely manner, within 5 business days of the study visit/assessment, the Investigator/Study Coordinator shall complete the eCRFs. When the Sponsor or designee requests additional data or clarification of data for the eCRF, the request must be answered satisfactorily in a timely manner.

12.4.2 Data Management and Archiving

The Sponsor will be responsible for the processing and quality control of the data. All source data, eCRFs, copies of protocols and protocol amendments, correspondence, subject identification lists (kept by the Investigator), informed consent forms, and other essential documents must be retained for a period of at least 2 years after the study completion or closure.

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

12.4.3 Direct Access to Source Data/Documentation

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

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

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

13 ETHICS

13.1 INFORMED CONSENT

Written informed consent will be obtained from each subject prior to the subject's medical record or personal health information being shared with any study representative. The subject's willingness to participate in the study will be documented in writing in a study-specific Informed Consent Form, which will be signed and dated by the subject or Legally Authorized Representative. The Investigator will keep the original consent form and a copy will be given to the subject. It will be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Subjects will be consented for two years or for the duration of the subject's participation in the study.

13.2 INSTITUTIONAL REVIEW BOARD (IRB)

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

The Sponsor must receive a copy of the IRB approval letter (or equivalent documentation) for the study protocol and Informed Consent Form before the site can be activated to enroll patients.

The IRB and Sponsor must approve any significant changes to the protocol, as well as a change of Principal Investigator. Documentation of IRB approval must be provided to the Sponsor. Records of all study review and approval documents must be maintained by the Investigator in the Study File/Regulatory Binder and are subject to inspection by the Sponsor (or designee) or regulatory authority during or after completion of the study.

The Investigator must notify the IRB, as per their reporting guidelines, and the Sponsor when he or she deviates from the protocol (see Section 11.3 above). The Sponsor must be notified of all relevant action taken by the IRB and must receive a copy of all study-related correspondence between the Investigator and the IRB.

The IRB must receive notification of study completion and a final report upon study completion or closure. A copy of these reports must be provided to the Sponsor. The Investigator must maintain an accurate and complete record of all submissions made to the IRB.

13.3 CONFIDENTIALITY REGARDING STUDY SUBJECTS

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

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRFs. A monitor or designee may conduct source-document verification on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential and handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

13.4 INDEPENDENT MEDICAL MONITOR

An independent Medical Monitor, an independent physician who is not a participant in the study, will review AEs that occur throughout the course of the study. The activities of the Medical Monitor will be guided by the Safety Plan. The Medical Monitor will be responsible for classifying events by severity, relationship, and seriousness, as well as whether they meet MAE criteria related to the primary safety endpoint. For the Primary Analysis, the Medical Monitor AE assessments will supersede those of the Investigators when there are differences.

13.5 CORE LABORATORY AND IMAGE TRANSFER

A central Core Laboratory will independently evaluate venographic imaging data collected at participating institutions. All protocol-required venograms must be sent to the Core Laboratory for evaluation. Refer to the Core Laboratory Imaging Manual for instructions for submitting data. IVUS images will also be sent to the Core Laboratory for possible future measurements.

13.6 PARTICIPATING INSTITUTIONS AND INVESTIGATORS

Study sites and Investigators will be selected based on a variety of factors including, but not limited to, experience with endovascular techniques, access to required facilities and equipment, sufficient and adequately trained personnel, and availability of potential subjects. The criteria used for determination will be documented.

13.7 INVESTIGATOR RESPONSIBILITIES

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

- Conducting the study in accordance with this investigational plan, signed agreements, and applicable regulations protecting the rights and safety of study subjects (e.g. IRB reporting requirements)
- Ensuring that informed consent is obtained for each study subject in accordance with the investigational plan
- Ensuring that IRB approval is secured prior to starting the study and ensuring continuing review and approval as required throughout the study
- Ensuring all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations, are adequately qualified and trained, and meet their commitments
- Maintaining adequate and accurate records and ensuring those records are available for inspection at any time
- Ensuring that conducting the study does not give rise to conflict of interest (financial disclosure is required)

14 ELECTRONIC DATA

Electronic data capture (EDC) will be utilized for data collection in this study. The study EDC will only be accessible to trained, authorized personnel with a unique user identifier and password used to access the system. Passwords will be set to expire periodically. Access to electronic study data will be provided to research personnel upon completion of training. Read and write access will be provided to registry sites but only for information and subject data at their own site. The CRO and Sponsor will have read-only access and can post queries for potential data-related discrepancies. Data will be reviewed, queried, cleaned and locked according to the study-specific Data Management Plan.

15 DEFINITIONS

The following definitions will be used throughout the course of the study:

Term	Definition
Primary Safety Endpoint Definitions	
Target venous segments (TVS)	The thrombus-containing venous segments, specified by the operator, that were treated with the study device at the index procedure. • These segments may include the popliteal vein, caudal femoral vein, cranial femoral vein, profunda/deep femoral vein, common femoral vein, external iliac vein, internal iliac vein, common iliac vein, or the inferior vena cava. • This includes segments that were treated with the study device, irrespective of the pre-procedure plan. • This does not include segments that were not intentionally treated but were instead passed through to remove the device from the leg
Primary Analysis population	The first 91 subjects with unilateral acute or subacute DVT of less than or equal to 6 weeks' duration, without recent (≤3 month) history of venous interventions.
Major adverse event (MAE)	A composite of events through 30 days that include all-cause mortality, major bleeding, new symptomatic PE documented by CTPA, or rethrombosis of a TVS in the Primary Analysis population.
MAE: All-cause mortality (≤30 days)	Death from any cause, irrespective of relationship to the device or to the procedure.
MAE: Major bleeding (≤30 days)	Clinically overt bleeding that is associated by a fall in the hemoglobin of ≥5 g/dL, transfusion of ≥2 units of red blood cells, or involvement of a critical site (e.g. intracranial or intraspinal). • Hemoglobinuria is not considered to be clinically-overt and, as such, would in and of itself not constitute major bleeding.
MAE: New symptomatic pulmonary embolism (PE) (≤30 days)	New PE accompanied by symptoms such as dyspnea, chest pain, or other localized symptoms referable to the event. • PE that is present at baseline but does not worsen by evidence with additional emboli confirmed via CTPA does not trigger the MAE definition. • New, symptomatic PE documented with CTPA but without a baseline imaging study will trigger the MAE.
MAE: Target vessel segment (TVS) rethrombosis (≤30 days)	Occlusive thrombosis of a TVS that occurs after patency had previously been restored in the segment, documented by imaging study such as duplex ultrasound, venography, computed tomographic venography, or magnetic resonance venography. • Rethrombosis requires imaging documentation of an open TVS at the end of after the index procedure, with imaging documentation of occlusion of the segment thereafter. • Rethrombosis can be device-related (for example, from vascular injury caused by the study device), or non device-related (for example, from inadequate anticoagulation).

Term	Definition
Primary Effectiveness Endpoint Definitions	
Technical success	Complete or near complete removal of venous thrombus from the TVS, as determined by the percent reduction in the Marder score for those segments. • When more than one venous segment is treated, the change in Marder score is calculated as the total score for the treated segments prior to intervention with the study device (baseline score) minus the total score after treatment with the study device but before treatment with any adjunctive devices or pharmacologic agents (post-treatment score), divided by the baseline score.
Additional Safety Definitions	
Adverse event (AE)	An AE is an untoward medical occurrence or exacerbation of an existing medical condition subsequent to treatment with the ClotTriever.
Serious adverse event (SAE)	An adverse event that meets at least one of the following: is fatal; is life-threatening; results in persistent or significant disability/incapacity; results in permanent impairment of a body function or permanent damage to a body structure; results in hospitalization or prolongs a hospitalization; or necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
Device-related event	An event that can be directly attributed to the use of the device, wherein, if the device functioned 100% to specifications and expectations, the event would not have occurred. • Rethrombosis in the absence of device induced vascular trauma (documented on an imaging study or with direct visualization of the vessel) is not device-related; rather it is a complication related to ineffective anticoagulation therapy. • Perforation from the study device is device-related, but perforation from a non-study adjunctive device is not. • As well, events that occur as a result of downstream venous compression (e.g., May-Thurner syndrome) are not considered device-related.
Procedure-related event	An event that is not device-related and occurs as a result of the procedure. • Events that occur ≤30 days of the index procedure or ≤30 days of a secondary procedure performed for a previous procedure-related complication, if the event is not device-related. • Examples include complications from ineffective anticoagulation (e.g. rethrombosis), excessive anticoagulation (e.g. bleeding), or vascular access with a non-study device (e.g. generic sheath, guidewire injury); distant complications (e.g. myocardial infarction, pneumonia); or contrast-induced complications (e.g. contrast-induced nephropathy or hypersensitivity reaction).
Reportable adverse event	Reportable AEs include all events considered in the safety analyses, all device- and/or procedure-related AEs, as well as any event resulting in death.
Minor bleeding	Bleeding that does not meet the MAE definition for Major Bleeding. • Mild oozing that occurs at an access puncture site and uncomplicated hemoglobinuria are not reported as minor bleeding events.

Term	Definition
Other Definitions	
Access site	The venous site used to gain access with the study device at the index procedure.
Adjunctive Therapy	Per CLOUT protocol, adjunctive therapy is defined as an additional thrombus removal strategy after ClotTriever thrombectomy has been completed (i.e. balloon, stenting, and placement of IVC filters during ClotTriever procedure session would NOT be considered adjunctive therapy).
Deep venous thrombosis (DVT)	Formation of thrombus within a deep vein, exclusive of non-thrombotic external compression or scarring of the wall.
Acute (DVT)	Suspected timeframe of the onset of DVT is ≤14 days previously, as determined by the Investigator.
Chronic DVT	DVT that, in the Investigator's opinion, began more than 6 weeks previously.
Distal DVT	Distal DVT occur in the veins of the calf, most frequently in the posterior tibial and peroneal veins, and less frequently in the anterior tibial and soleal/gastrocnemius veins.
Patency	Primary patency means that you perform a procedure to restore patency to a vessel, and report how long patency is maintained without any repeat intervention. Primary-assisted patency defines the durability of an intervention that failed initially but not to the level of thrombosis and was retreated. Secondary patency means that the initial intervention failed to the level of thrombosis and was retreated. Once the second treatment was successfully performed, secondary patency defines the durability of that second intervention.
Proximal DVT	Proximal DVT is defined when the process involves the iliac, deep femoral, or popliteal veins.
Subacute DVT	DVT that, in the Investigator's opinion, began >14 days but ≤6 weeks previously.
Target limb	The limb referable to the TVS. In the case of bilateral treatment, both limbs are target limbs.

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APPENDIX 1 KNOWN RISKS OF THROMBECTOMY

Event Category	Event
Cardiac	Myocardial infarction
	Congestive heart failure
	Arrhythmia
	Hypertension
	Hypotension
Wound	Wound infection
	Wound pain
	Wound dehiscence
	Serous wound drainage
	Lymphorrhea
	Hematoma
	Ecchymosis
Peripheral vascular	Vessel perforation
	False aneurysm formation
	Arterial dissection
	Mural thrombus formation
	Vessel occlusion
	Arteriovenous fistula
	Distal embolization
Venous	Deep venous thrombosis
	Pulmonary embolism
	Paradoxical embolization
Cerebrovascular	Transient ischemic attack
	Stroke
	Intracranial hemorrhage
Pulmonary	Exacerbation of chronic lung disease
	Respiratory failure
Miscellaneous	Sepsis
	Death

SIGNATURE APPROVAL PAGE

CLotTriever **OUT**comes (**CLOUT**) Registry
Protocol Number: 18-001
Version: 9.0
August 12, 2020

Signed:  Aug 12, 2020

Keith Hebert
Senior Director, Clinical Research
Inari Medical