SAFETY AND EFFECTIVENESS STUDY OF THE ANGIOSAFE PERIPHERAL CTO CROSSING SYSTEM (RESTOR-1)

PROTOCOL AND STATISTICAL ANALYSIS PLAN (SAP) SUMMARY

PROTOCOL NUMBER: 0071

NCT NUMBER: NCT04663867

SPONSOR:

ANGIOSAFE, INC.

PROTOCOL VERSION: 06

SAP VERSION: 01

DATE: DECEMBER 22, 2025

STUDY SYNOPSIS

A synopsis of the study is presented in **Table 1**.

Table 1: Study Synopsis

Sponsor Name:	AngioSafe, Inc.("AngioSafe")
Title of Study:	Safety and Effectiveness Study of the AngioSafe Peripheral CTO Crossing System (RESTOR-1)
Objective:	To demonstrate the safety and effectiveness of the AngioSafe Peripheral CTO Crossing System to facilitate crossing chronic total occlusions (CTOs) in the peripheral arteries of lower limbs.
Name of Investigational Device:	AngioSafe Peripheral CTO Crossing System
Indications for Use:	The AngioSafe Peripheral CTO Crossing System is intended to facilitate the intraluminal placement of guidewires beyond stenotic lesions, including chronic total occlusions (CTOs) in the peripheral vasculature.
Design:	This is a prospective, single-arm, multi-center pivotal study assessing the safety and effectiveness of the AngioSafe Peripheral CTO Crossing System. This system facilitates the crossing of chronic total occlusions (CTOs) in the common femoral artery (CFA), superficial femoral artery (SFA), and popliteal artery, and allows for placement of a guidewire in the distal true lumen.
Planned Enrollment:	To evaluate the primary endpoint, a minimum of 70 subjects will be treated at up to 20 sites.
Subject Population:	Adult men and women ≥ 22 years of age with peripheral vascular disease and symptoms of intermittent claudication/critical limb ischemia and a CTO in the lower extremity to which the symptoms can be attributed.
Clinical Sites:	Up to 20 study centers within the United States will participate.
Length of Subject Follow-Up:	All subjects will be followed for 30 days (± 7 days) after their procedure.
Study Duration:	The duration of the study will be approximately six (6) months from the date of the first subject's consent to the last subject's 30-day follow-up completion.

Inclusion Criteria:	1. Subject is able and willing to comply with protocol requirements, has been informed of the nature of the study, and has signed the IRB-approved informed consent form. 2. Subject is ≥ 22 years of age at the time of enrollment/consent. 3. Subject has peripheral arterial disease as defined by the Rutherford Clinical Classification (Category 2 "Moderate claudication" through Category 5 "Minor tissue loss – nonhealing ulcer, focal gangrene with diffuse pedal ischemia"). 4. Peripheral artery disease in the affected extremity is confirmed by imaging including at least one of the following: catheter-based angiography, computed tomographic angiography (CTA), and/or magnetic resonance angiography (MRA). **Note:** Duplex ultrasound should not be the sole imaging modality to confirm subject eligibility.
Angiographic Inclusion Criteria:	1. Subject's target lesion is in native de novo common femoral artery (CFA), superficial femoral artery (SFA), and/or popliteal artery. 2. Reference vessel diameter(s) for subject's target lesion is ≥ 3.0mm and ≤ 10mm by visual estimate. 3. Subject's target lesion is a severely stenosed segment of ≤ 200mm that involves the CTO(s). 4. Subject's target lesion involves at least one CTO, i.e., is deemed as total occlusion (100% stenosis). 5. Subject has at least one patent tibial vessel (≤ 70% stenosis) with run-off to the foot. **Note:** Only one target lesion per subject may be treated in the study, regardless of whether it is a contiguous occlusion or if there is intermittent reconstituted flow with multiple CTOs. In the case of bilateral disease with eligible lesions on both sides, one target lesion may be enrolled in the study if clinically indicated. Although the subject's target lesion length should be no more than 200mm, this does not preclude a total treated length of greater than 200mm at the discretion of the investigator.
Exclusion Criteria:	1. Subject has a systemic infection or an infection in the extremity of the target lesion. 2. Subject's target lesion is within native vein or synthetic vessel grafts or is in-stent occlusion. 3. Subject's contralateral limb requires planned intervention concurrently with the study procedure. 4. Subject's target limb requires intervention of a chronic total occlusion in the inflow vessels concurrently with the study procedure. 5. Subject requires planned intervention of the lower extremities after the study procedure within the timeframe for the 30-day follow-up visit. 6. Subject has a known coagulopathy or bleeding diatheses, thrombocytopenia with platelet count less than 50,000/µl, or INR > 1.7

	(unless corrected prior to procedure, as verified by a lab test no older than 5 days prior to the investigational procedure). 7. Subject in whom antiplatelet, anticoagulant, or thrombolytic therapy is contraindicated. 8. Subject has known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-treated. 9. Subject has known allergy to nickel, titanium, urethane, nylon, or silicone. 10. Subject has history of myocardial infarction within 30 days prior to enrollment/consent. 11. Subject has history of stroke within 30 days prior to enrollment/consent. 12. Subject has chronic kidney disease (CKD) of stage 4 or greater based on an Estimated Glomerular Filtration Rate (eGFR) <30ml/Min. 13. Subject has baseline hemoglobin levels <10g/dL verified by a lab test no older than 14 days prior to enrollment. 14. Subject is pregnant or nursing, for females of child-bearing potential (< 50 years of age). 15. Subject is participating in another interventional research study that may interfere with study endpoints. 16. Subject has limited life expectancy or co-morbid conditions, or social/psychological problems that, in the opinion of the Investigator, will preclude them from participation and completion of study procedures or requirements. 17. Subject has had prior major amputation (above ankle) in the extremity that is being treated. 18. Subject is presenting with acute limb ischemia (ALI). 19. Subject has had a prior unsuccessful attempt to cross the target lesion.
Primary Endpoint:	Clinical Success of the AngioSafe Peripheral CTO Crossing System to facilitate placement of a guidewire into the distal true lumen of a femoropopliteal artery CTO, in the absence of device-related major adverse events through discharge or 24 hours post-procedure, whichever is sooner.
Secondary Endpoints:	1. Technical Success of the AngioSafe Peripheral CTO Crossing System. Technical Success is defined as the ability of catheter to facilitate placement of a guidewire into the distal lumen. 2. Procedural Success is defined as Technical Success without a procedural complication within 30 days after the procedure. Procedural complication is defined as the need for open or repeat endovascular surgical repair in the treated limb, or a major bleeding event as defined by Bleeding Academic Research Consortium (BARC) criteria 3 – 5.

	3. Evaluation of intraluminal CTO crossing facilitated by the AngioSafe Peripheral CTO Crossing System, as assessed by an Intravascular Ultrasound (IVUS). 4. The primary endpoint in the subgroup of the degree of calcification (none/focal/mild/moderate, severe).
Safety Endpoints:	1. Frequency of device-related MAEs through discharge or 24 hours following the procedure, whichever is sooner. 2. Frequency of MAEs at 30 days.
Ancillary Endpoints:	1. Performance of the AngioSafe Peripheral CTO Crossing System defined as the following: a. Pre-treatment assembly of the catheter over the guidewire and into the guide catheter without damage or kinking. b. Delivery of the device, guidewire, and guide catheter assembly to the desired location, i.e., proximal to the proximal cap of the CTO. c. Extension and expansion of the Centering System out of the guide catheter. d. Ability of the device to penetrate the proximal cap. e. Ability to place a guidewire in the true vessel lumen distal to the target CTO. 2. Lesion crossing time defined as: time starting from the placement of the Peripheral CTO Crossing System at the proximal cap to the time the guidewire is placed in the distal true vessel lumen. 3. Rutherford Clinical Classification assessment at 30 days versus baseline. 4. Pain Numeric Rating Scale (NRS) assessment at 30 days versus baseline. 5. Healthcare services utilization/billing assessment for peripheral CTO treatment procedure (e.g., number of accessories used/expense, fluoroscopy time/expense, catheter lab time/expense, medications used/expense).
Statistical Analysis:	Primary endpoint analysis: The primary analysis will be performed by comparing the device result to the performance goal at a one-sided 0.05 level of significance using the exact test based on the binomial distribution.
Sample Size and Power:	In Banerjee et al., the technical success rate of the CTO crossing device group was 0.74 (184/248) (CI: 0.68, 0.80)[1]. The primary endpoint of clinical success (defined as technical success without a device-related MAE through discharge or 24 hours post-procedure, whichever is sooner) of the AngioSafe Peripheral CTO Crossing System is expected to be 0.85. The null hypothesis is that the AngioSafe Peripheral CTO Crossing System will perform better than 0.70, which is within the lower bound of the 95% confidence interval of the technical success rate of the CTO crossing device group reported by Banerjee et al. (CI: 0.68, 0.8). The primary endpoint null and alternative hypotheses of interest are: H0: $\pi \leq 0.70$ vs. Ha: $\pi > 0.70$. Assuming the true performance is 0.85,

	at α 1-sided =0.05 and a power of 90%, the sample size estimate for the binomial exact test is 70. Only one target lesion per subject may be treated in the study. If data are submitted by a study center on more than one lesion in a subject, the lesion to be included in the study will be chosen at random. Where an analysis is presented for treated subjects, the indicated sample size numbers (N or n) represent the number of treated subjects, which corresponds to the number of treated lesions.
Analysis Sets:	FULL ANALYSIS SET (FAS): the FAS will consist of all enrolled subjects who have the AngioSafe CTO Crossing System inserted into the vasculature. The FAS population will be the primary analysis population for the primary effectiveness evaluation. PER-PROTOCOL ANALYSIS SET (PP): the PP analysis set is a subset of the FAS and will consist of all patients for whom no major protocol deviations (no deviations which may affect the study effectiveness outcome) is documented. In identifying this population, major protocol deviations are identified prior to database lock as those impacting the interpretation of the data. The PP analysis set may be used to provide supportive data for the effectiveness analyses of primary and secondary endpoints if those analyses using the FAS set produce unexpected results.
Statistical Methods:	All statistical procedures will be completed using SAS® version 9.4 or higher. The analyses of all endpoints will include relevant descriptive statistics. Continuous variables will be summarized by number of observations (N), mean (m), standard deviation (SD), and 95% confidence interval of the mean (95% CI). If the data are skewed or otherwise non-normal, the median and IQR will also be reported. Categorical variables will be summarized by N, the proportion in each category (pi), and 95% CI of each pi. Count variables will be summarized as continuous or categorical variables, depending on the number of unique counts. Generally, 5 or fewer counts will be treated as categorical and more than 5 as continuous. Time-to-event variables will be summarized as the proportion of subjects experiencing an event at a series of relevant time points (pi), the N, and the 95% CI. These proportions will be estimated by Kaplan- -Meier analysis with covariates). For summary purposes, if not otherwise specified, the baseline value of a parameter is defined as the last non-missing assessment prior to the procedure. All patient data, including those derived, will be presented in individual patient data listings. All listings will be sorted by patient ID, date/time, and visit. Data listings will be based on all available data.

SUMMARY OF STUDY DESIGN

This is a prospective, single-arm, multi-center pivotal study assessing the safety and effectiveness of the AngioSafe Peripheral CTO Crossing System. This system facilitates the crossing of chronic total occlusions (CTOs) in the common femoral artery (CFA), superficial femoral artery (SFA), and popliteal artery, and allows for placement of a guidewire in the distal true lumen.

- Eligibility will be evaluated and subjects will be enrolled (consented) based on medical history and prior diagnosis of peripheral arterial disease (PAD) and peripheral CTO in accordance with institutional routine clinical care practices (symptoms, laboratory findings, diagnostic angiography, and/or other modalities employed per the institutional standard of care).
- Screening imaging will be reviewed by a central Screening Committee to approve each subject's participation in the study. Imaging reviewed by the committee should include at least one of the following: catheter-based angiography, computed tomographic angiography (CTA), and/or magnetic resonance angiography (MRA). Imaging should generally be current within the last 90 days prior to Screening Committee submission. Imaging older than 90 days, or duplex ultrasound of high quality may be sufficient to receive conditional approval by the Screening Committee, with the requirement that final eligibility must be verified by the Investigator based on the pre-procedure angiogram on the day of the index procedure.
- Upon consent, the research staff will perform baseline assessments, document subject eligibility and schedule the PTA procedure within an approximately 1-week timeframe, and no more than 30 days from the time of the baseline assessment. Subjects who have recently had vascular interventions in the target limb or contralateral limb may be enrolled in the study, though their investigational procedure must be deferred for 30 days or more from the date of the previous intervention. Baseline assessments and the investigational procedure must be scheduled accordingly.
- On the day of the procedure, a pre-procedure angiogram of the target lesion will be performed to confirm CTO length, percent of stenosis, reference vessel diameter, and target vessel tortuosity, and to verify final subject eligibility based on the angiographic inclusion criteria.
- The investigational device will be prepped per the Instruction for Use (IFU) and positioned at the target lesion. A guidewire will be advanced across the distal cap and into the distal true lumen.
- The device will be removed and an IVUS catheter will be introduced over the guidewire, advanced into the track made by the device passage and intraluminal disposition of the track will be recorded.
- The IVUS catheter will be removed and the target lesion will be treated either with a balloon and/or stent and/or atherectomy, at the discretion of the investigator.
- Cine-angiography will capture the entire procedure.

- Patients will be monitored and followed through discharge and 30 days post-procedure.

BIBLIOGRAPHY

[1] Banerjee S, Jeon-Slaughter H, Tsai S, et al. Comparative Assessment of Procedure Cost and Outcomes Between Guidewire and Crossing Device Strategies to Cross Peripheral Artery Chronic Total Occlusions. JACC Cardiovasc Interv. 2016;9(21):2243-2252