CLotTriever **OUT**comes (CLOUT)

Statistical Analysis Plan

Version 2.0

Study Treatment Device: ClotTriever® Thrombectomy System

Protocol No.: 18-001

Study Phase: Observational, non-Interventional

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APPROVAL

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LIST OF ABBREVIATIONS AND DEFINITIONS

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. Description of 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[1]
- 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 5)

2. 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 are subsets of the approximately 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 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, 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.

2.1. Primary Safety Endpoint

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.

2.2. Primary Effectiveness Endpoint

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).

2.3. 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)

3. Analysis Populations

3.1. Full Analysis Population

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.

3.2. Primary Analysis Population

The Primary Analysis dataset is a subset of subjects with unilateral acute or subacute DVT of less than or equal to a 6-week 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.

4. Incomplete Date Handling and Missing Data

Incomplete dates will follow the following imputation assignment rules:

1. If day is missing but month and year are present, the day will be set to the first date of the month.
2. If both day and month are missing but year is present, then January 1st will be used as the imputed value.
3. If year is missing, then the date is considered missing. In general, missing data points are not imputed.

Subjects with missing effectiveness data will be assumed to have data missing at random and will be imputed by random selection with replacement of data from subjects with pre- and post-intervention measurement of thrombus removal. By repeating this process, e.g. for 5,000 separate data replicates, an empirical distribution of primary effectiveness endpoint can be derived for an estimated 95% confidence interval based on the quantiles of the empirical distribution. The robustness of the multiple imputation outcome will be tested with a tipping point analysis encompassing all possible imputation outcomes.

5. Statistical Methods and Analysis

5.1. 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 1**).

Assuming 5% attrition over 30 days, enrollment of 91 subjects is necessary for the Primary Analytic Dataset.

Table 1. 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 2**). 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 2. 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%.

5.2. Derivation of Performance Goal

5.2.1. Derivation of the Safety Performance Goal

The primary safety endpoint of 30-day MAE was available from the following seven studies, summarized in **Table 3**.

Table 3. Safety Performance Goal Literature Summary

Study	Year	Subjects	MAE (%)
Lin	2017	89	35 (39.3%)
Vedantham	2017	336	12 (3.6%)
Schweitzer	2000	50	1 (2.0%)
Elsharawy	2002	18	0 (0%)
Enden	2011	90	13 (14.4%)
Mewissen*	1999	473	60 (12.7%)
Mewissen	1999	312	75 (24.0%)
Engelberger	2015	48	2 (4.2%)
Total Weighted Average		1,104†	198 23.8%‡

** The second row for the Mewissen study is included to tabulate rethrombosis rate, which was specified for the 312 subjects with acute DVT alone.*

†The total number of subjects does not include the 312 subjects in the acute cohort of the Mewissen publication, since this is a subset of the 473 subjects in the series.

‡The MAE weighted average was calculated individually using a random effects model for each component of the composite endpoint and then summed to derive the weighted average for the composite MAE endpoint. For this reason, the denominator for the weighted average is not 1,104, nor does the MAE weighted average represent a simple weighted average of the MAE rates of the individual publications.

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, is 34%.

5.2.2. Derivation of the Effectiveness Performance Goal

The primary effectiveness endpoint of Technical Success was assessed from published studies that treated DVT with pharmacologic means or with other thrombectomy devices (**Table 4**). 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%.

Table 4. Effectiveness Performance Goal Literature Summary

Study	Year	Subjects	Subjects with Near Complete Thrombus Removal
Elsharawy	2002	18	11 (61.1 %)

Enden	2011	90	68 (75.6 %)
Vedantham*	2017	202	69 (34.2 %)
Engelberger	2015	48	29 (60.4 %)
Mewissen	1999	312	96 (30.8 %)
Schweizer	2000	50	10 (20.0 %)
Total Weighted Average		720	283 39.3%
** The Vedantham data point was derived from a conference presentation, additional sensitivity analysis will be performed to re-calculate the weighted average of the performance goal without this data point.*			

5.3. 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 rate 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 MAE rate will be compared to a performance goal with the following null and alternative hypotheses:

$$H_0: P_S \geq PG_S \text{ versus } H_A: P_S < PG_S$$

where P_S is the proportion of subjects with 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.

5.4. 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[a] and will be compared to a performance goal with the following null and alternative hypotheses:

$$H_0: P_E \leq PG_E \text{ versus } H_A: P_E > PG_E$$

where P_E is the proportion of subjects with Technical Success, defined as complete or near complete removal of thrombus with the study device, measured by a venographically-determined reduction of ≥75% in the Marder score in the TVSs. The effectiveness performance goal, PG_E, is Technical Success defined in the same manner, derived from published literature.

a 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.

5.4.1. Sensitivity Analysis

The primary effectiveness performance goal will be re-calculated by removing the Vedantham data point from Table 4. As such, the weighted average Technical Success rate was 41.3%. Using a 10% margin and rounding to the next percent, the performance goal for the primary effectiveness endpoint of Technical Success was 32%. This performance goal will be used in the sensitivity analysis for the primary effectiveness endpoint.

5.5. Secondary Endpoints Analysis

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

5.6. Data Poolability Assessment

The planned analysis for this study will pool data across clinical study sites. Efforts were made to ensure that consistent procedures were used across study sites, including use of the same study protocol, Sponsor monitoring the sites for compliance, and use of identical data-gathering instruments. The appropriateness of pooling the data across centers will be evaluated.[2, 3] Baseline characteristics will be compared 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, comparing the primary endpoints across sites after adjusting for covariate differences. Logistic regression model will be utilized to include unbalanced covariates and sites as an independent variable, and the study outcome as dependent variable to assess outcome differences. 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.

6. References

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2. Localio AR, Berlin JA, Ten Have TR, Kimmel SE. Adjustments for center in multicenter studies: an overview. Ann Intern Med. 2001 Jul 17;135(2):112-23. doi: 10.7326/0003-4819-135-2-200107170-00012. PMID: 11453711.
3. Paul P. Gallo (2000) CENTER-WEIGHTING ISSUES IN MULTICENTER CLINICAL TRIALS, Journal of Biopharmaceutical Statistics, 10:2, 145-163, DOI: 10.1081/BIP-100101019