Study Title: **FL**owTriever for **A**cute **M**assive Pulmonary **E**mbolism (FLAME)

Statistical Analysis Plan

Version 3.0

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Study Title: **FL**owTriever for **A**cute **M**assive Pulmonary **E**mbolism (FLAME)

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Name of Study Device: FlowTriever® Retrieval/Aspiration System

Protocol No.: 20-001

Study Phase: Observational, non-Interventional

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Approval

This document has been reviewed and approved by:		
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Director, Head of Biostatistics and Programming	Signature	Date

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Term
AC	Anticoagulation
BARC	Bleeding Academic Research Consortium
CEC	Clinical events committee
CPR	Cardiopulmonary resuscitation
ECMO	Extracorporeal membrane oxygenation
FLAME	FlowTriever for Acute Massive Pulmonary Embolism
FT	FlowTriever
GLM	Generalized linear models
ICU	Intensive care unit
IV	Intravenous
PE	Pulmonary embolism
PG	Performance Goal
SAP	Statistical Analysis Plan

1. Description of Study Objectives

The primary objective of the FLAME observational study is to evaluate treatment outcomes of patients diagnosed with high-risk pulmonary embolism who have received treatment with the FlowTriever System (FlowTriever Arm) compared to an established performance goal (PG).

In addition to the primary objective, outcomes of patients diagnosed with high-risk (massive) pulmonary embolism who have received treatment with other (non-FlowTriever) therapies will also be analyzed.

2. Study Design

The FLAME study is a prospective, multicenter, non-randomized, parallel group, observational study of subjects with high-risk pulmonary embolism concurrently enrolled in the FlowTriever, Context, and Prior Therapy Arms of the study. FlowTriever Arm patients will be the primary population utilized to evaluate the study Primary and Secondary Endpoints for study success. These endpoints will also be evaluated in the Context Arm population in a descriptive manner and will not be used to determine study success.

2.1. Primary Objectives

To compare the treatment outcomes for patients who received FlowTriever against a historical performance goal. The treatment outcomes are assessed during a patient's in-hospital period for the index treatment of the high-risk pulmonary embolism.

2.2. Primary Endpoint

In-hospital composite endpoint of:

- All-cause mortality
- Bailout to an alternative thrombus removal strategy
- Clinical deterioration
- Major bleeding, BARC 3b/3c/5a/5b definition

Table 1: Primary Endpoint Definitions

Primary Endpoint Definitions	Bailout to an alternate thrombus removal strategy	Need for mechanical circulatory support or another thrombus removal strategy after the primary treatment strategy was initiated. The additional treatment strategy was not an a priori part of the original treatment plan (conceived beforehand). All bailout events will be adjudicated by the CEC.
	Clinical Deterioration	• Need for CPR • Need to start IV vasopressors to keep systolic blood pressure > 90 mmHg in a previously normotensive patient • Need for mechanical ventilation in a previously spontaneously breathing patient • Need for noninvasive positive pressure ventilation in a patient previously on nasal cannula
	Major Bleeding, BARC 3b/3c/5a/5b	• 3b: Overt bleeding plus hemoglobin drop of ≥ 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade, bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid); bleeding requiring intravenous vasoactive agents • 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal), subcategories confirmed by autopsy or imaging or lumbar puncture, intraocular bleed compromising vision. • 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious • 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

2.3. Secondary Endpoints

Secondary endpoints include safety endpoints as well as utility measures which will be assessed in the FlowTriever Arm. Details of the secondary endpoints are provided in **Table 2** below. These endpoints will also be evaluated in the Context Arm population in a descriptive manner and will not be used to determine study success.

Table 2: Secondary Endpoint Definitions

Secondary Endpoints	**Secondary Safety Endpoints** • Frequency of each primary endpoint composite component • Frequency of stroke (ischemic or hemorrhagic) • Frequency of device-related complications

	• Access site injury requiring intervention, both venous and arterial **<u>Utility Measures</u>** • Length of hospital stay • Length of ICU stay • Use of ECMO, including either pre- or post-treatment initiation and duration • Time to extubation, if intubated • Discharge location

3. Analysis Populations

3.1. FlowTriever Arm

Up to 71 subjects will be enrolled in the FlowTriever Arm. FlowTriever Arm subjects are defined as those subjects where FlowTriever is used as the primary treatment for pulmonary embolism.

An interim analysis is planned for the first 50 subjects enrolled into the FlowTriever Arm. Based upon the interim analysis (as described in **Section 5.5**), a decision will be made whether to continue enrollment.

3.2. Context Arm

Subjects with high-risk pulmonary embolism who are treated with non-FlowTriever therapies (as the primary treatment for PE) will be enrolled concurrently with subjects in the FlowTriever arm. Context-arm therapies may include but are not limited to; thrombolysis (either systemic or catheter directed), anticoagulation, surgical thrombectomy, and non-FlowTriever percutaneous thrombectomy. The Context Arm enrollment will have at least 1:1 ratio as compared with the FlowTriever Arm, therefore at least 71 subjects would be in the Context Arm population.

3.3. Prior Therapy Arm

Data collection for Prior Therapy Arm subjects will include information surrounding the PE treatment, progression to High-Risk PE, and patient course through hospital discharge. Safety data will also be collected, but not CEC adjudicated or analyzed as outlined for the FlowTriever and Context Arm subjects. Subjects receiving prior advanced treatment for low/intermediate-risk PE in the same hospital setting as a second treatment for high-risk PE likely have a different profile than those receiving advanced care for the first time after diagnosis of high-risk PE, and therefore should be looked at separately. In the spirit of the AHA guidelines for trial design in this patient population, data will be collected to ensure representation of this smaller yet significant group of high-risk PE patients and will be reported in a descriptive manner.

4. Incomplete Date Handling and Missing Data

Incomplete dates will be handled with the following imputation 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 imputed value.
3. If year is missing then the date is considered missing. In general, missing data points are not imputed.

Other missing data will not be imputed.

5. Statistical Methods and Analysis

5.1. Sample Size

The sample size of the FlowTriever arm is calculated using a two-stage group sequential design, where the FlowTriever arm is expected to have a rate of in-hospital composite endpoint of all-cause mortality, bailout to an alternative thrombus removal strategy, clinical deterioration, and major bleeding (BARC 3b/3c/5a/5b definition) of 18%. The rate of the FlowTriever arm composite endpoint is compared with the historical performance goal of 32%, based on meta-analysis results shown in **Table** . A one-sided binomial proportion's test with normal approximation is used against the performance goal with a power of 80% and a one-sided $\alpha = 0.05$; O'Brien Fleming boundary was implemented where the first stage, or interim analysis, is planned at N = 50 subjects enrolled and consequently arriving at the second stage, or final analysis, with N = 71 subjects as shown in **Table** .

Table 3: Sample Size 2-stage Group Sequential Design

Analysis Stage	N	Z-score Threshold	P-value Threshold	FT Event proportion	Significant event number
Interim	50	-2.0311	0.0211	0.186	≤9.3
Final	71	-1.7116	0.0435	0.225	≤16.0

5.2. Derivation of Performance Goal

The primary safety endpoint performance goal was derived from the following 22 studies, summarized in **Table** .

Table 4: Safety Performance Goal Literature Summary

First Author	Subjects	In-Hospital ACM	Bailout to Alternative Thrombus Removal Strategy	Clinical Deterioration (within 24 hours)	Major Bleeding (BARC3b/3c/5a/5b)
Avgerinos et al. 2017	90	15/90, 16.6%	NS	NS	24/90, 26.6%
Barrett et al. 2010	SE: 9	6/9, 66.6%	NS	NS	NS
	TL: 10	6/10, 60.0%			
	AC: 14	5/14, 35.7%			

First Author	Subjects	In-Hospital ACM	Bailout to Alternative Thrombus Removal Strategy	Clinical Deterioration (within 24 hours)	Major Bleeding (BARC3b/3c/5a/5b)
Carvalho et al. 2010	16	7/16, 43.8%	NS	NS	NS
Cho et al. 2016	19	NS	4/19, 21.0%	NS	NS
	26		NS		
Corsi et al. 2017	17	NS	NS	NS	NS
de Winter et al. 2019	33	NS	8/33, 24.2%	NS	NS
George et al. 2018	32	15/32, 46.9%	NS	5/32, 15.6%	NS
Hartman et al. 2015	24	NS	NS	NS	NS
Kuo et al. 2015	28	4/28, 14.3%	NS	NS	0/28, 0.0%
Minakawa et al. 2018	63	23/63, 36.5%*	NS	NS	NS
Moon et al. 2018	Without ECMO: 9	7/9, 77.8%	NS	NS	NS
	ECMO:14	8/14, 57.1%			7/14, 50.0%
Munakata et al. 2012	10	3/10, 30.0%†	NS	NS	2/10, 20.0%
Neely et al. 2015	49	5/49, 10.2%*	NS	NS	1/49, 2.0%
Niwa et al. 2012	289	NS	NS	NS	NS
Pasrija et al. 2018	Control: 27	5/27, 18.5%	NS	NS	3/27, 11.1%
	Protocol: 29	1/29, 3.4%			4/29, 13.8%
Roncon et al. 2018	47	NS	NS	NS	NS
	30				
Secemsky et al. 2019	46	15/46, 32.6%	NS	NS	11/46, 23.9%
Senturk et al. 2016	186	NS	NS	NS	10/186, 5.4%
Sharifi et al. 2016	23	2/23, 8.7%	NS	NS	0/23, 0.0%
Shiomi et al. 2017	31	4/31, 12.9%	NS	NS	NS
Ucar et al. 2013	107	18/107, 16.8%	NS	NS	4/107, 3.7%
Wang et al. 2010	20	NS	12/20, 60.0%	NS	NS
	20		4/20, 20.0%		
Total	**1,318**	**149/607**	**28/92**	**5/32**	**66/609**
Weighted Average [95% Confidence Intervals]	**NA**	**28.5% [20.6%, 37.9%]**	**30.3% [15.5%, 50.7%]**	**15.6% [6.7%, 32.5%]**	**11.5% [6.0%, 21.0%]**

AC, Anticoagulation; ACM, All-Cause Mortality; BARC, Bleeding Academic Research Consortium; ECMO, Extracorporeal Membrane Oxygenation; NA, Not Applicable; NS, Not Specified; SE, Surgical Embolectomy; TL,

First Author	Subjects	In-Hospital ACM	Bailout to Alternative Thrombus Removal Strategy	Clinical Deterioration (within 24 hours)	Major Bleeding (BARC3b/3c/5a/5b)
Thrombolytic Therapy					
**Operative mortality was reported. Only patients in refractory shock were included in the analysis.*					
†All patients died within 15 hours of the procedure.					

The PG is a weighted average calculated from each individual component of the composite endpoint; each component is a result of a meta-analysis across previous publications using the random-effects model. The PG weighted average is 21.5%, and by using a 10% margin with rounding up to the nearest percent, the PG for the study is 32%.

5.3. Primary Endpoint Analysis

The primary endpoint is the in-hospital composite endpoint of all-cause mortality, bailout to an alternative thrombus removal strategy, clinical deterioration, and major bleeding (BARC 3b/3c/5a/5b definition) from the FlowTriever arm. The rate of the composite endpoint is expected to be 18% and compared with performance goal of 32%:

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

where Ps is the proportion of subjects with in-hospital composite endpoint and PG_S is the performance goal of proportion of subjects with in-hospital composite endpoint derived from previous publications and expert opinions on subjects who were non-FlowTriever treatments.

The one-sided binomial's proportion test with normal approximation would be used at a one-sided $\alpha = 0.05$. Primary endpoint analysis can be carried out at interim analysis and/or final analysis stage.

5.4. Secondary Endpoint Analysis

Secondary Endpoints include both Secondary Safety Endpoints and Utility Measures as listed below:

Secondary Safety Endpoints

- Frequency of each primary endpoint composite component
- Frequency of Stroke (ischemic or hemorrhagic)
- Frequency of device-related complications
- Access site injury requiring intervention, both venous and arterial

Utility Measures

- Length of hospital stay
- Length of ICU stay
- Use of ECMO, including either pre- or post-treatment initiation and duration
- Time to extubation, if intubated
- Discharge location

Descriptive statistics will be used for secondary endpoints for both the FlowTriever Arm and Context Arm populations. Continuous variable will report min, max, mean, SD, IQR, Q1, Q3 etc. as deemed

appropriate. Categorical variable will report frequency counts and percentage. Time-to-event variable may be reported with Kaplan-Meier and/or Cox proportional hazards model estimates.

Additional exploratory analyses on secondary endpoints may include confounder adjustment in generalized linear models (GLMs) and may be specified in separate SAPs.

5.5. Interim Analysis

The interim analysis population will be N = 50 enrolled subjects in the FlowTriever arm with adjudicated in-hospital composite endpoint. Primary endpoint analysis method in **Section 5.3** will be used on the interim analysis population to decide whether the study should be stopped early due to achieving early decision rule based on primary endpoint. The $|z-score|$ threshold is 2.031, which translates to in-hospital composite endpoint proportion being ≤ 0.186. Therefore, having ≤ 9 in-hospital composite endpoint events out of N = 50 patients may qualify for stopping the study early and conclude achieving significant difference from PG_S = 32% (see **Table**).

Secondary endpoint analysis may be conducted in a descriptive fashion without hypothesis testing, therefore not spending any Type I error (α).

5.6. Context Arm Analysis

The Context Arm may be analyzed with methods mentioned in primary and secondary endpoint analyses along with descriptive statistics and will not be used to determine study success.

5.7. Prior Therapy Arm Analysis

The Prior Therapy Arm may be analyzed using descriptive statistics.