Statistical Analysis Plan

Version 3.0

27-May-2021

for

FLowTriever All-Comer Registry for Patient Safety and Hemodynamics (FLASH)

Clinical Investigation Plan No.: 18-002

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List of Abbreviations and Definitions

Abbreviation	Term
AE	Adverse event
AHA	American Heart Association
BSA	Body surface area
CI	Cardiac index
CO	Cardiac output
CRO	Contract research organization
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomographic pulmonary angiography
DOAC	Direct oral anticoagulant
DVT	Deep venous thrombosis
ECMO	Extracorporeal membrane oxygenation
H-FABP	Heart type fatty acid binding
HIT	Heparin-induced thrombocytopenia
ICF	Informed consent form
IRB	Institutional review board
ITT	Intent to treat
LV	Left ventricle
MAE	Major adverse events
mMRC	Modified Medical Research Council Dyspnea Scale
PAPi	Pulmonary Artery Pulsatility Index
PE	Pulmonary embolism
PEmb-QOL	Pulmonary Embolism Quality of Life
PHI	Protected Health Information
PESI	Pulmonary Embolism Severity Index
RV	Right ventricle
RV/LV	Right ventricular to left ventricular diameter ratio
RVSWI	Right ventricular stroke work index
SAE	Serious adverse event
SAP	Statistical analysis plan
SIV	Site initiation visit
sPESI	Simplified Pulmonary Embolism Severity Index
SVI	Stroke volume index
TPVR	Total pulmonary vascular resistance
UAT	Ultrasound-accelerated thrombolysis
VTE	Venous thromboembolism

1.0 DESCRIPTION OF STUDY OBJECTIVES

The primary study objective is to evaluate the safety and effectiveness of the FlowTriever System for use in the removal of emboli from the pulmonary arteries in the treatment of acute pulmonary embolism (PE). The use of the device will be assessed in a real-world population, with eligibility criteria that closely approximate its use in clinical practice.

2.0 STUDY DESIGN

The FLASH Registry is a prospective, single-arm, multicenter study of the FlowTriever System for intermediate-risk (submissive) and high-risk (massive) PE. The Registry will collect data on demographics and comorbidities; details from the PE diagnosis and treatment; and clinical outcomes through six months follow-up. Up to 1000 patients (up to 800 in the US and up to 200 in Europe and UK) with PE will be enrolled at up to 100 Registry sites (up to 70 in the US, up to 30 in Europe and UK).

A Conservative Therapy Substudy, with up to 300 additional patients with anticoagulation treatment as the initial planned primary treatment strategy for intermediate-risk PE, will be evaluated in the US only. The Conservative Therapy Substudy will collect data on demographics and comorbidities; details from the PE diagnosis and treatment; and clinical outcomes through six months of follow-up.

All patients will have follow-up evaluations after the index procedure (Full Analysis Population), or after primary treatment of anticoagulation is administered at baseline (Conservative Therapy Substudy), at 48 hours (+ 36 hours), 30 days(+ 15 days), and six months (+ 90 days).

In addition to the follow-up schedule, approximately 100 patients receiving treatment with the FlowTriever System and approximately 100 patients receiving anticoagulation treatment as their primary treatment for PE will be asked to participate in ongoing data collection for 6 months utilizing an Apple Watch (for US only patients). Patients will be provided with a pre-configured Apple Watch with cellular capabilities at the 48 hour visit. Patients will be expected to wear the Apple Watch daily, with data collection occurring through their 6 month visit.

2.1. Primary Safety Endpoints

The primary endpoint is the rate of Major Adverse Events (MAE). MAEs are defined as a composite, when one or more of the following events occur:

- Device-related mortality through 48 hours after the index procedure
- Major bleeding through 48 hours after the index procedure
- Intraprocedurele device- or procedure-related adverse events (AEs), including:
  - Clinical deterioration defined by hemodynamic or respiratory worsening, or
  - Device-related pulmonary vascular injury, or
  - Device-related cardiac injury

2.2. Secondary Endpoints

The secondary endpoints of the study will assess safety, effectiveness, and utility measures, as follows.

2.2.1. Secondary Safety Endpoints

- Individual components of the MAE composite endpoint
  - Device-related death through 48 hours after the index procedure
  - Major bleeding through 48 hours after the index procedure, summarized by commonly used scales and each individual element of each scale
  - Clinical deterioration defined by hemodynamic or respiratory worsening
  - Device-related pulmonary vascular injury
  - Device-related cardiac injury
- Major access site complications requiring open surgical or endovascular intervention or blood transfusion
- All-cause mortality within 30 days
- Device-related serious AEs within 30 days

2.2.2. Secondary Effectiveness Endpoints

- Reduction in pulmonary artery pressures during the procedure
- Hemodynamic improvements during the procedure, including cardiac index (CI) and stroke volume index (SVI), right ventricular stroke work index (RVSWI), pulmonary artery pulsatility index (PAPi) and total pulmonary vascular resistance (TPVR)
- Reduction in right-ventricular/left-ventricular (RV/LV) ratio from baseline to 48 hours, 1 month, and 6 months; as measured by CT or echocardiography

2.2.3. Utility Measures

- Fluoroscopy time
- Contrast used
- Estimated blood loss during the index procedure
- Thrombectomy time

- Length of intensive care unit stay, if any
- Length of total hospital stay

2.3. Exploratory Analysis

Exploratory analysis will calculate descriptive statistics for baseline demographics, other outcomes of interest, and stratified by subpopulations.

3.0 ANALYSIS POPULATION

3.1. Full Analysis Population

Up to 1000 patients enrolled in the FLASH registry.

3.2. Conservative Therapy Substudy

Up to 300 additional patients with anticoagulation treatment as the initial planned primary treatment strategy for intermediate-risk PE (US patients only).

3.3. Wearables Follow-up Subpopulation

Approximately 100 patients receiving treatment with the FlowTriever System and approximately 100 patients in the Conservative Therapy Substudy, who participated in the Apple Watch substudy (US patients only).

4.0 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 imputed value.
3. If year is missing, then the date is considered missing.

In general, complete case analysis will be used to handle missing values and no other missing data points other than dates will be imputed.

5.0 STATISTICAL METHODS AND ANALYSIS

5.1. Sample Size

The sample size of up to 1000 patients reflects an adequate size to accrue data on the real-world use of FlowTriever System for PE, as assessed in up to 100 Registry sites (up to 70 in the US, up to 30 in Europe and UK).

5.2. Primary, Secondary, and Exploratory Endpoint Analysis

This is an observational study and as such is not hypothesis-driven. The endpoints will be assessed for patients in the Full Analysis Population, and Conservative Therapy Substudy, with descriptive statistics. Continuous variables will report any combination of mean, median, Q1, Q3, IQR, minimum and maximum, while the categorical variables will report frequency count and percentages (%). Crude p-values may be reported for descriptive statistics; paired continuous outcomes will use Wilcoxon Signed-Rank Test while paired categorical outcomes will use McNemar's Test.

6.0 DOCUMENT VERSION HISTORY

REV	DESCRIPTION OF CHANGE
1.0	New Release
2.0	Updated to include Conservative Therapy and Apple Watch
3.0	Updated to be in alignment with CIP version 8.0