# *EVALUATION OF FLUID VOLUME IN PATIENTS WITH SEPSIS AND REFRACTORY HYPOTENSION*

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| **Protocol Number:** | PRO-0001 |
| **Date/Version:** | October 30, 2017 / Version H |
| **Study Product:** | Noninvasive Starling™ SV |
| **Sponsor:** | Cheetah Medical, Inc.™<br>1320 Centre Street<br>Newton, MA 02459 |

This clinical investigation is performed in accordance with applicable guidelines, standards and regulations. This report template is based on ISO 14155:2011 Clinical Investigation Plan (annex A).

[redacted]

## 1. CONTENTS

## INVESTIGATOR'S STATEMENT AND SIGNATURE

The signing of this protocol by the Principal Investigator signifies that the contents have been laid down in full agreement and that the study will be conducted according to this protocol, its amendments, the clinical trial agreement and the applicable regulatory requirements.

***Investigator approval:***
***I have read this protocol and agree that it contains all the necessary information required to conduct the study, and I agree to conduct it as described. I understand that this study will not be initiated without appropriate Institutional Review Board (IRB) approval and that the administrative requirements of the governing body will be fully complied with.***

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|---|---|
| Principal Investigator's Signature | Date |
| Principal Investigator's Printed Name | |
| Site Name | Site # |

## 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AKI | Acute kidney injury |
| BP | Blood pressure |
| CPR | Cardiopulmonary resuscitation |
| CRF | Case report form |
| CV | Curriculum vitae |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| ICC | Intraclass correlation |
| ICF | Informed consent form |
| ICU | Intensive Care Unit |
| IRB | Institutional Review Board |
| ITT | Intention to treat |
| IV | Intravenous |
| L/min | Liter per minute |
| mITT | Modified intent to treat |
| PLR | Passive leg raise |
| PPV | Pulse Pressure Variation |
| RRT | Renal replacement therapy |
| SAE | Serious adverse event |
| SV | Stroke volume |
| SVI | Stroke volume index |
| SVV | Stroke volume variation |
| TFC | Thoracic fluid content |
| TPRI | Total peripheral resistance index |
| VET | Ventricular ejection time |

## 3. SYNOPSIS

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| **Title:** | Evaluation of fluid volume in patients with sepsis and refractory hypotension |
| **Short Title:** | **FRESH** (Fluid Responsiveness Evaluation in Sepsis-associated Hypotension) Fluid Trial |
| **Investigational Device:** | Noninvasive Starling™ SV |
| **Objective:** | To assess the mean difference in fluid balance and associated patient outcomes, based on a dynamic assessment of fluid responsiveness in septic patients with refractory hypotension in an ICU setting. |
| **Design:** | Multi-center randomized study comparing dynamic assessment of fluid responsiveness utilizing Starling SV compared to a control group.<br><br>Subjects will be randomized in a 2:1 treatment to control group ratio to increase power for sub-analysis by patient population.<br><br>Patients randomized to the Starling SV arm will have treatment guided by a dynamic assessment of fluid responsiveness (measured by a change in stroke volume index > +10%) as assessed by passive leg raise (PLR).<br><br>Patients randomized to the control group will receive standard of care treatment. The use of dynamic fluid assessment (i.e. SVV, PPV, or SV change) to determine fluid responsiveness is prohibited. |
| **Primary Endpoint:** | Mean difference in fluid balance (L) at 72 hours or ICU discharge, whichever occurs first, between the two treatment groups |
| **Secondary Endpoints** | 1. Length of ICU stay (days) until subject is medically ready for discharge<br>2. Number of hours free from ventilator use<br>3. Requirement for mechanical ventilation<br>4. Number of hours free from vasopressor use<br>5. Changes in serum creatinine levels from baseline<br>6. Requirement for renal replacement therapy (RRT)<br>7. Mean volume of fluid between the two treatment groups<br>8. Incidence of Major Adverse Cardiac Event (MACE)<br>9. Incidence of Adverse Events (AE)<br>10. Number of ICU readmissions<br>11. 30 day in-hospital mortality rate<br>12. Discharge location<br>13. Mean difference in fluid balance at ICU discharge |

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| **Planned Enrollment:** | Approximately 210 subjects will be involved in the analysis population |
| **Population:** | Patients with sepsis who exhibit refractory hypotension (MAP < 65, or require treatment with vasopressors to maintain a MAP > 65) following initial fluid resuscitation (1L of fluid). |
| **Follow-up Schedule:** | Hemodynamic data collection will occur for a 72 hour period starting at the time of study enrollment. Subject outcome data will be collected until the time of hospital discharge. |
| **Number of Sites:** | Between 7-15 clinical sites located in the US and 1-3 sites located in the UK |
| **Sub Analysis:** | Primary and secondary endpoints will also be evaluated by the following secondary analysis:<br>• Patient disease state<br>• Patients determined to be fluid responsive vs non-fluid responsive<br>• AKI measures in patients determined to increase serum creatinine levels from baseline<br>• Enrollment time frame<br>Additional sub-analysis will be run as appropriate. |
| **Inclusion Criteria:** | 1. Diagnosis of sepsis, as exhibited by 2 or more of the following SIRS criteria and a known or presumed infection at time of screening:<br>o Temperature of > 38 C or < 36 C<br>o Heart rate of > 90/min<br>o Respiratory rate of > 20/min or PaCO2 < 32 mm Hg (4.3 kPA)<br>o White blood cell count > 12000/$mm^3$ or < 4000/$mm^3$ or >10% immature bands<br>2. Refractory hypotension (either one single reading of MAP <65 exhibited during the evaluation period, or requiring treatment with vasopressors to maintain a MAP > 65) despite initial fluid resuscitation (1L of treatment fluid)<br>3. Patient enrolled in study within 24 hours of arrival to the hospital<br>4. Anticipated ICU admission. Patients may be maintained on another unit (such as within the ER or a step down unit) during the 72 hour monitoring period if the treatment algorithm is adhered to during this time period.<br>5. Able to provide signed informed consent or consent can be obtained from the patient's authorized representative |
| **Exclusion Criteria:** | 1. Primary diagnosis of: acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, major cardiac arrhythmia, drug overdose, or injury from burn or trauma<br>2. Known aortic insufficiency, or aortic abnormalities |

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| | 3. Hemodynamic instability due to active hemorrhage (e.g. gastrointestinal bleeding / coagulopathy / trauma)<br>4. Patient has received >3 liters of IV fluid prior to study randomization<br>5. Requires immediate surgery<br>6. Patient transferred to the ICU from another hospital unit<br>7. Do not attempt resuscitation (DNAR or DNR) order<br>8. Advanced directives restricting implementation of the resuscitation protocol<br>9. Contraindication to blood transfusion<br>10. Attending clinician deems aggressive resuscitation unsuitable<br>11. Transferred from another in-hospital setting<br>12. Not able to commence treatment protocol within 1 hour after randomization<br>13. Known intraventricular heart defect, such as VSD or ASD<br>14. Use of additional hemodynamic monitoring involving SVV, PPV, or SV change to determine fluid responsiveness<br>15. Seizure in the last 24 hours<br>16. Prisoner<br>17. Pregnancy<br>18. Age <18<br>19. Known allergy to sensor material or gel<br>20. Inability or contraindication to doing a passive leg raise with both extremities, such as inability to interrupt venous compression boots<br>21. Patient has an epidural catheter in place<br>22. Suspected intra-abdominal hypertension<br>23. Inability to obtain IV access<br>24. Diabetic ketoacidosis<br>25. Hyper-osmolarity syndrome<br>26. Patient treatment uncouples from the treatment algorithm<br>27. Patient should be excluded based on the opinion of the Clinician/Investigator |
| **Statistical Design:** | Variables will be tabulated using descriptive statistics. Continuous variables will be presented as number, mean, and standard deviation with 95% confidence intervals, as well as medians and ranges. For categorical variables, relative frequencies and 95% confidence intervals will be provided. Any survival analyses performed will utilize the Kaplan-Meier method.<br><br>All tests for continuous endpoints utilize a two-sided t-test for difference in two independent means at the overall 0.05 level of significance.<br><br>The study will be conducted under a common protocol. To evaluate differences among investigational sites in the trial, summary tables by site will be presented and compared. |

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| | Results from the sites will be pooled only if there are no statistical differences between the sites (95% confidence). If variables are found to differ by investigational site, then the variable and/or study site may be identified for special consideration in subsequent analyses. |
| **Sponsor/ Manufacturer:** | Cheetah Medical, Inc<br>1320 Centre Street<br>Newton, MA 02459 |

# 4. INTRODUCTION

## 4.1 Background

Hemodynamic optimization of critically ill patients is a goal for clinicians in order to afford the patient the best possible outcomes. Being able to precisely and rapidly determine patient fluid responsiveness provides the bedside physician and nursing staff the information needed to make critical decisions in regards to the patient's fluid status and management of additional fluids and medications. Patient management in the ICU is complex and multiple studies and meta-analyses have shown that clinicians struggle to diagnose which patients will benefit from fluid administration (i.e. the administration of intravenous fluids will increase cardiac output).[1] The findings show that up to 50% of patients in the ICU will not benefit from fluid administration.[2] Studies have also shown that excessive fluid administration and fluid retention leads to poorer outcomes.[3-5] Well-timed decision making with accurate information is critical and challenging particularly in the setting of a patient with sepsis.

As fluid management and cardiac output determination are linked to better decision-making and improved outcomes in ICU, the use of a dynamic assessment of fluid responsiveness becomes a key tool for patient management. The Noninvasive Starling SV device, which is FDA cleared and CE marked, is currently in clinical use and can be used to provide a dynamic assessment of fluid responsiveness. This study will show the clinical utility of initiating an assessment of patient fluid responsiveness prior to the administration of treatment fluid.

# 5. STUDY JUSTIFICATION

This study is designed to highlight the benefits of treatment guided by dynamic measures using the Starling SV within the population of patients diagnosed with sepsis and refractory hypotension. To confirm this, treatment and outcome data will be compared between patients randomized to receive treatment guided by a dynamic assessment of fluid responsiveness, compared to the current standard of care treatment.

# 6. DEVICE

## 6.1 Device Description

Cheetah Medical's Noninvasive Starling SV is a portable, non-invasive, cardiac output detector system. The Starling SV system measures the cardiac output by employing electrical bioreactance. Bioreactance is a measure of the electrical characteristics of a volume of tissue and fluid. In the case of cardiac output measurements, the relevant tissue includes the heart and the immediate surrounding volume of the thorax. The relevant fluid is blood.

Cheetah Medical's Starling SV electrode is a double electrode sensor. Within each sensor, one electrode is used to transmit a high frequency sine wave into the body, while the resulting voltage is measured at the adjacent electrode. Four electrodes are placed at specific areas of the thorax, the impedance to the current flow calculated, and the electrical bioreactance waveform constructed. This information is used to determine cardiac output. The Starling SV device also measures and displays associated hemodynamic parameters based on calculations of measurements already incorporated into the Starling SV device. These parameters are: Cardiac Index (CI), Ventricular Ejection Time (VET), Total Peripheral Resistance Index (TPRI), Stroke Volume Index (SVI), Stroke Volume Variation (SVV), Cardiac Power (CP), Cardiac Power Index (CPI) and Thoracic Fluid Content (TFC). Fluid responsiveness is indicated by a change in SV of > +10% in response to a fluid challenge.[6]

## 6.2 Device Accountability

The Starling SV system (monitor and electrode disposables) will be supplied by Cheetah Medical to each investigational site.

## 6.3 Device Indication for Use

The Starling SV with NIBP and SpO2 functionalities is a portable, hemodynamic monitoring non-invasive Cardiac Output monitoring device that monitors and displays a patient's Cardiac Output (CO) in Ltr/Min with a Non Invasive Blood Pressure (NIBP) function that non-invasively measures and displays blood pressure (diastolic, systolic and mean arterial pressure) and heart rate and with a SpO2 function that non-invasively measures and displays blood oxygen saturation (SpO2). The device displays associated hemodynamic parameters based on measurements or calculations of measurements already incorporated into the Starling SV. These parameters are:

- Cardiac Index (CI),
- Stroke Volume (SV),
- Stroke Volume Index (SVI),
- Stroke Volume Variation (SVV),
- Heart Rate (HR),
- Ventricular Ejection Time (VET),
- Total Peripheral Resistance (TPR),
- Total Peripheral Resistance Index (TPRI),
- Cardiac Power (CP),
- Cardiac Power Index (CPI),
- Blood Oxygenation (SPO2)
- Oxygen Delivery Index (DO2I),

- Electrical impedance of the chest cavity (Z0),
- Thoracic Fluid Content (TFC),
- Thoracic Fluid Content change from preset time period (TFCd) and
- Thoracic Fluid Content from baseline (TFCd0).
- Changes in SV, CO and other hemodynamic parameters which are derived by Bioreactance® as a result of posture

The Starling SV with NIBP and SpO2 functionalities is intended for use within hospitals and other healthcare facilities (e.g., outpatient clinics) that provide patient care).

### 6.4 Device Procedure(s)/Training

All sites will receive device training on the Cheetah Starling SV system prior to study initiation.

### 6.5 Fluid Assessment-Passive Leg Raise (PLR)

The passive leg raise (PLR) shall be followed according to the following guidelines:

- Select PLR Test from main menu on Starling SV system
- With patient in semi-recumbent position (30-45°), obtain three minutes of monitoring for average baseline SVI
- With patient legs raised to 45 degree angle, obtain three minutes of monitoring for peak SVI value
- Fluid responsiveness is indicated by a $\Delta$ SVI $\geq$ +10%

## 7. INVESTIGATIONAL DESIGN

### 7.1 Study Objective

The objective of this study is to assess the mean difference in fluid balance at 72 hours or ICU discharge, whichever occurs first, and associated patient outcomes, based on a dynamic assessment of fluid responsiveness in septic patients with refractory hypotension in an ICU setting.

### 7.2 Study Design

This study is a prospective, multi-center, randomized trial comparing the mean difference in fluid balance and associated patient outcomes between a treatment guided by a dynamic assessment of fluid responsiveness and a standard of care control group not using dynamic fluid assessment. Between seven and fifteen sites will be used to enroll 210 subjects with the diagnosis of sepsis and refractory hypotension and in whom the Starling SV system can be attached. Subjects will be randomized in a 2:1 treatment to control group ratio. In the treatment group, a dynamic assessment of fluid responsiveness will be performed at every clinical decision point to treat hypoperfusion or impending hypoperfusion for the first 72 hours of study enrollment. Examples of a clinical decision point include a MAP of < 65, SBP < 90 or blood pressure that is rapidly trending lower, low urine output, or any other clinical indication to administer/alter fluid bolus or pressors. Additionally, an assessment of fluid responsiveness will be performed every 12 hours if no clinical assessments have taken place during this time period.

Fluid responsiveness will be assessed using a passive leg raise (PLR) to guide corresponding treatment (**Appendix A**). Continuous data will be collected from the Starling SV system during the entire treatment period. In the control group, no required therapeutic protocol will be used for patient treatment, and is determined per the discretion of the physician and hospital standards. The use of dynamic fluid assessment (i.e. SVV, PPV, or SV change) to determine fluid responsiveness within the control group is prohibited.

## 7.3 Study Endpoints

### *7.3.1 Primary Endpoint*

The primary endpoint is an evaluation of the difference (L) between the two treatment groups mean fluid balance at 72 hours or ICU discharge, whichever occurs first. The following hypothesis will be tested:

$$Ha: \mu c - \mu_T \neq 0$$

where μt and μc is the average fluid balance in the Starling SV and control groups, respectively.

### *7.3.2 Secondary Endpoints*

Secondary endpoints to be evaluated:

1. Length of ICU stay (days) until subject is medically ready for discharge
2. Number of hours free from ventilator use
3. Requirement for mechanical ventilation
4. 
5. Number of hours free from vasopressor use
6. Changes in serum creatinine levels from baseline
7. Requirement for renal replacement therapy (RRT)
8. Mean volume of fluid between the two treatment groups
9. Incidence of Major Adverse Cardiac Event (MACE)
10. Incidence of Adverse Events (AE)
11. Number of ICU readmissions
12. 30 day in-hospital Mortality rate
13. Discharge location
14. Mean difference in fluid balance at ICU discharge

## 7.4 Study Duration

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|---|---|
| Estimated Study Start: | Q3 2016 |
| Estimated Enrollment Completion: | Q2 2018 |
| Estimated Final Report: | Q3 2018 |

# 8. SUBJECT POPULATION AND SELECTION

## 8.1 Subject Population

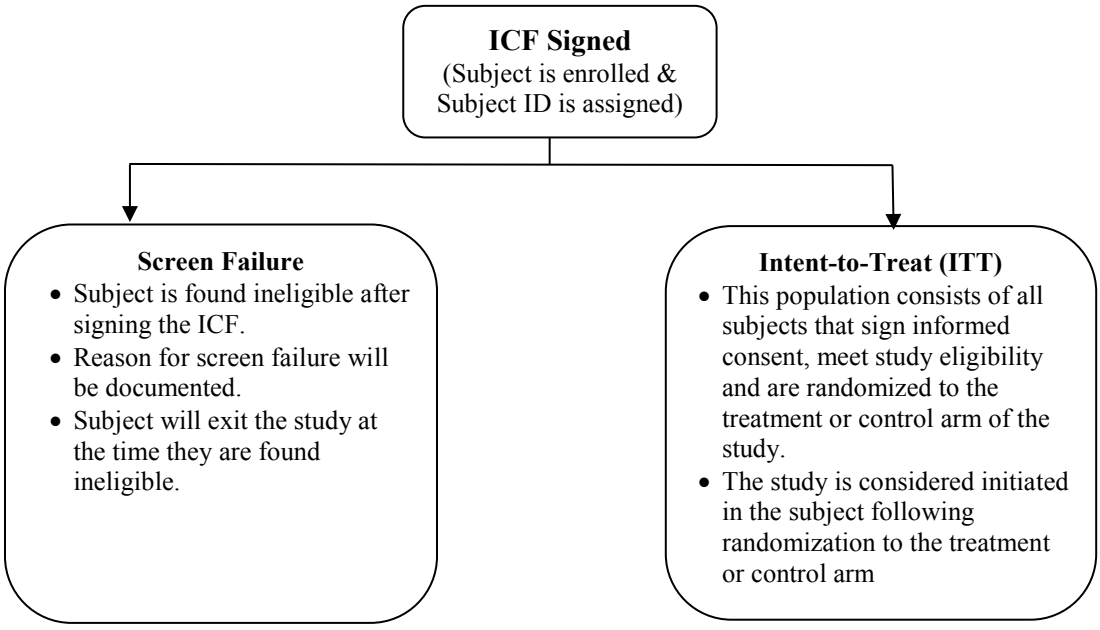
Adult subjects with the diagnosis of sepsis and refractory hypotension will be considered as a candidate for the study. A maximum of 210 subjects enrolled and in the analysis population will be included in the study. Subjects will be considered to be enrolled when they or their designated representative sign the informed consent form (ICF).

Subjects who are enrolled will be assigned a subject ID. Subjects that sign the ICF, but are found ineligible will be considered screen failures and will be exited from the study at that time. Enrolled subjects who meet study eligibility will be included in the analysis populations and are further described in **Section 12**.

The diagnosis of sepsis is defined as a known or presumed infection and the presence of 2 or more SIRS criteria as detailed in **Section 8.2**. Refractory hypotension is defined as the presence of hypotension following initial resuscitation with 1L of fluid. After obtaining ICF and confirming that the inclusion and exclusion criteria are met, the Cheetah sensors will be placed and connected to the Starling SV monitor. Useable readings will be confirmed prior to initiating the study data collection period.

A diagram outlining the overall subject enrollment plan is shown below:

**Figure 1: Subject Flow Diagram**



## 8.2 Inclusion Criteria

Subjects must meet the following inclusion criteria:

1. Diagnosis of sepsis, as exhibited by 2 or more of the following SIRS criteria and a known or presumed infection at the time of screening:
   - Temperature of > 38 C or < 36 C
   - Heart rate of > 90/min
   - Respiratory rate of > 20/min or PaCO2 < 32 mm Hg (4.3 kPA)
   - White blood cell count > 12000/$mm^3$ or < 4000/$mm^3$ or >10% immature bands
2. Refractory hypotension (either one single reading of MAP <65 exhibited during the evaluation period, or requiring treatment with vasopressors to maintain a MAP > 65) despite initial fluid resuscitation (1L of treatment fluid)
3. Patient enrolled in study within 24 hours of arrival to the hospital
4. Anticipated ICU admission. Patients may be maintained on another unit (such as within the ER or a step down unit) during the 72 hour monitoring period if the treatment algorithm is adhered to during this time period.
5. Able to provide signed informed consent or consent can be obtained from the patient's authorized representative

## 8.3 Exclusion Criteria

Subjects must not have any of the following exclusion criteria:

1. Primary diagnosis of: acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, major cardiac arrhythmia, drug overdose, or injury from burn or trauma
2. Known aortic insufficiency, or aortic abnormalities
3. Hemodynamic instability due to active hemorrhage, (e.g. gastrointestinal bleeding/coagulopathy/trauma)
4. Patient has received >3 liters of IV fluid prior to study randomization
5. Requires immediate surgery
6. Patient transferred to the ICU from another hospital unit
7. Do not attempt resuscitation (DNAR or DNR) order
8. Advanced directives restricting implementation of the resuscitation protocol
9. Contraindication to blood transfusion
10. Attending clinician deems aggressive resuscitation unsuitable
11. Transferred from another in-hospital setting
12. Not able to commence treatment protocol within 1 hour after randomization
13. Known intraventricular heart defect, such as VSD or ASD
14. Use of additional hemodynamic monitoring involving SVV, PPV or SV changes to determine fluid responsiveness
15. Seizure in the last 24 hours
16. Prisoner
17. Pregnancy

18. Age <18
19. Known allergy to sensor material or gel
20. Inability or contraindication to doing a passive leg raise with both extremities, such as inability to interrupt venous compression boots
21. Patient has an epidural catheter in place
22. Suspected intra-abdominal hypertension
23. Inability to obtain IV access
24. Diabetic ketoacidosis
25. Hyper-osmolarity syndrome
26. Patient treatment uncouples from the treatment algorithm

27. Patient should be excluded based on the opinion of the Clinician/Investigator

## 8.4 Subject Screening

All subjects diagnosed with sepsis and refractory hypotension will be considered potential candidates. All subjects screened for the study will be captured on the site's Screening Log. The log will capture the subject's gender, age, date of screening and the reason(s) for study exclusion.

## 8.5 Informed Consent Procedures

Written informed consent on the approved IRB informed consent form must be obtained for all subjects who are potential study candidates before any study specific tests or procedures are performed. Due to the high likelihood of the subject's critical clinical state and therefore the possibility of their inability to provide informed written consent, the subject's designated representative will be acceptable to provide written informed consent.

The general process for obtaining informed consent shall:

- Ensure that the principal investigator or his/her authorized designee conducts the informed consent process;
- Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation;
- Avoid any coercion or undue improper influence on, or inducement of, the subject to participate;
- Not waive or appear to waive the subject's legal rights;
- Use native non-technical language that is understandable to the subject;
- Provide ample time for the subject, or designee, to read and understand the informed consent form and to consider participation in the clinical investigation;
- Include personally dated signatures of the subject and the principal investigator or an authorized designee responsible for conducting the informed consent process;
- Provide the subject, or designee, with a copy of the signed and dated informed consent form and any other written information required per Site's Institutional Policy (i.e. additional HIPAA language).

## 8.6 Subject Randomization

Subjects will be randomized to either the treatment or control arm of the study once the decision has been made to admit the patient to the ICU. Any patients that are enrolled but are not admitted to the ICU, or who receive > 3L of treatment fluid prior to randomization will be considered a screen failure and will be exited from the study at this time.

Subjects will be randomized in a 2:1 treatment to control ratio to increase power for sub-analysis by patient population. Additionally, subject randomization will be stratified to ensure even randomization between the three time windows of enrollment (0-6 hours, 6-12 hours, 12-24 hours)

## 8.7 Subject Discontinuation/Withdrawal Criteria

Once the subject has been enrolled in the study, she/he may withdraw her/his consent to participate in the study at any time without prejudice. Participation in this clinical investigation is entirely voluntary. Likewise, there may be a reason identified by the Investigator that deems the subject no longer suitable for the study. In either case, the Investigator will contact Cheetah Medical to discuss the circumstances for discontinuation/withdrawal. Discontinuation or withdrawal may occur for any of the reasons listed below (this list is not all inclusive).

1. Subject is uncooperative with compliance of required study tests and/or medical management
2. Investigator determines that subject has developed a condition in which continued participation in the study is considered potentially harmful to the subject
3. Subject withdraws their consent
4. Adverse event which is considered intolerable by the patient, their LAR of the Principal Investigator
5. Subject has a significant protocol violation
6. Subject incorrectly enrolled in the study
7. Cheetah Medical terminates the study

### *8.7.1 Subjects Lost to Follow-Up*

Subjects may be considered lost to follow-up for the following reasons:

- During data analysis, data indicates there is unacceptable bias in the measurements
- Data collection is interrupted prior to 72 hour data collection period of ICU stay
- Severe agitation and/or cardiopulmonary resuscitations resulted in poor quality data

# 9. STUDY PROCEDURES

## 9.1 Baseline Assessments

After written informed consent is obtained, baseline assessments will be made to further determine the subject's eligibility for the study. Data collected will include:

- Demographics
- Age
- Medical history

- SOFA assessment
- Physical exam, limited
- Hemoglobin and blood gas (per chart review, if available)
- Serum creatinine level
- Lactate level (per chart review, if available)
- Urine sample (to be frozen for possible future testing)
- Optional plasma serum collection (two, 5ml samples to be frozen for possible future testing)
- Current medications

## 9.2 Enrollment Procedure

Assuming the subject meets all study eligibility criteria, the investigator, or designees, will place the Cheetah device (Starling SV) on the subject. The device will be evaluated for obtaining the optimum expected hemodynamic readings before the study is begun according to the Starling SV Instructions for Use (IFU). This is done to confirm that data collected from the monitoring devices will be evaluable. It is recommended that approximately 15-20 minutes are allowed for the device to autocalibrate and achieve a stable baseline prior to beginning any measurements at the initiation of the study.

If the Starling SV does not provide the expected hemodynamic recordings, it will be adjusted or replaced as needed until it provides the expected recordings. If it is determined that the device will not provide the expected recording, then the subject will be withdrawn from the study.

## 9.3 Data Collection Procedure

When the Starling SV is determined to be providing the expected waveforms and recordings, the study device data collection period will begin. Recorded information will be collected and stored by the device. After the data collection period has ended the data will be downloaded and used for analysis.

### *9.3.1 Hemodynamic Collection Methods*

**Starling SV:** Following the Instructions for Use, the Starling SV device will be connected to the subject by placing four of the system's sensors on the subject's chest: left and right mid-clavicle and left and right mid-last ribs. The device will undergo 1 minute of autocalibration after which measurements will begin to be obtained. Data from the device is available as a visible read-out on the monitor screen and stored internally. At the conclusion of the data collection period, the data will be downloaded and provided to the sponsor or designee.

### *9.3.2 Fluid Assessment*

A fluid assessment will be initiated at the following time points:

- Baseline (at study enrollment)
- At every clinical decision point for the first 72 hours of study enrollment. Examples of a clinical decision point include the decision to give additional fluid volume, or escalate vasopressors.

- MAP <65 during first 72 hours of study enrollment

A fluid assessment will be administered using a passive leg raise according to **Section 6.5**.

### *9.3.3 Additional Data Collection*

Other data points and associated times will be collected in addition to the analysis of the continuous data from the Starling SV system. Types of data points for collection are:

- Medical history
- Medications
- Volume of treatment fluid administered
- Urine output (to be recorded every 12 hours)
- Respiratory status
- Serum Creatinine level (every 24 hours +/- 4 hours , for 72 hour monitoring period and at 30 day discharge)
- Lactate level (per chart review, if available)
- Significant clinical events not previously identified for study data collection, e.g. cardiac arrest, CPR, intubation, extubation, placement of catheters (intravenous, arterial, urinary, etc), etc.
- Changes in mechanical ventilator status parameters

## 9.4 Schedule of Assessments

Each subject will follow a schedule of assessments and events from which data will be collected (Table 1).

**Table 1: Schedule of Assessments**

| Assessment/Event | Pre-Consent | Consent | Baseline | Enrollment-72 hours | 72 hours-Discharge |
|---|---|---|---|---|---|
| Subject Identification | X | | | | |
| Determine Eligibility | X | | | | |
| Informed Consent | | X | | | |
| Medical History | | | X | X | X |
| Physical Exam, limited, and lab values | | | X | | |
| Urine Sample | | | X | | |
| Optional plasma serum collection (two, 5ml samples to be frozen for possible future testing) | | | X | | |
| Serum Creatinine | | | X | X | X (chart review) |
| Medications, specific | | | X | X | X |
| Volume resuscitation fluid | | | X | X | |
| Respiratory Status | | | X | X | X |

| Assessment/Event | Pre-Consent | Consent | Baseline | Enrollment-72 hours | 72 hours-Discharge |
|---|---|---|---|---|---|
| (intubated, ventilated) | | | | | |
| Starling SV System | | | Attached | Continuous hemodynamic recordings | |
| Fluid Assessment | | | | X | |
| Adverse events | | | | X (+48 hours) | |

# 10. SAFETY/DEVICE ASSESSMENT

## 10.1 Adverse Events

Subjects will be carefully monitored during the study for possible device related adverse events (AEs). The investigator or designee will determine AE occurrences and collect the required data. It is anticipated that the occurrence of device related adverse events will be a low number. All device related adverse events will be reviewed not only by the site investigator, but also by the sponsor's medical officer.

Serious Adverse events will be collected during the 72 hour (**+ 48 hours**) treatment period in the following areas: Cardiac, CNS, pulmonary, renal, and skin disorders.

### *10.1.1 Device Related Adverse Event (AE)*

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons occurring as a result of the study device

### *10.1.2 Serious Adverse Events*

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death
- Led to serious deterioration in the health of the subject, that either resulted in:
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient or prolonged hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- Led to fetal distress, fetal death or a congenital abnormality or birth defect

## 10.2 Reporting Procedures

### *10.2.1 General Reporting Requirements*

All device related adverse events must be recorded on the Adverse Event eCRF by the investigator (or designee). The report should include: start date of the adverse event, treatment,

resolution, and assessment of both the seriousness and the relationship to the investigational device.

The following criteria must also be adhered to by the Investigator:

- Completion of separate device related Adverse Event forms to document each event
- The forms must be signed by the Investigator, and
- Supplying to the Sponsor (or designee), upon Sponsor's request, with any additional information related to the safety reporting of a particular event

### *10.2.2 Reporting Requirements of SAEs*

All serious adverse events must be reported by the investigator by submitting the Adverse Event eCRF within 24 hours of learning of the adverse event.

The Investigator shall:

a) Report to the IRB serious adverse events per the institutional requirements for timing and amount of support information,
b) Supply the Sponsor (or designee), upon Sponsor's request, with any additional information related to the safety reporting of a particular event.

### *10.2.3 Sponsor Reporting*

All adverse events will be reported to the applicable regulatory authority as required per applicable regulatory authority.

Cheetah Medical, or their designee is responsible for the classification and reporting of adverse events and applicable regulatory requirements.

## 11. STUDY MONITORING

The study will be monitored according to Cheetah Medical's monitoring procedures. A study specific monitoring plan will be developed to ensure protocol compliance and applicable regulatory requirements.

Clinical monitors will be designated by Cheetah Medical. Monitors will verify subject data and ensure compliance with GCP, clinical protocol and other study requirements to be utilized for the study.

### 11.1 Monitor Training

All Cheetah Medical designated monitors will be trained appropriately to monitor study progress including but not limited to the protocol and CRFs.

### 11.2 Site/Investigator Training

Cheetah Medical will be responsible for providing training to the investigator and appropriate clinical site personnel.

### *11.2.1 Protocol Training*

Training on study protocol requirements will be provided for the entire study team at the initiation of the study. It is ultimately the responsibility of the Investigator to ensure all clinical site personnel participating in this study are adequately trained.

To ensure uniform data collection and protocol compliance, Cheetah Medical and/or designee will perform study initiation visits to review the clinical protocol, techniques for the identification of eligible subjects, instructions on in-hospital data collection, and methods for soliciting data from alternative sources.

### *11.2.2 Device Training*

This procedure may only be performed by qualified investigators, familiar with the Cheetah Medical system. Training on the Starling SV system will be performed and documented for the site Investigator who is responsible for using the device, by the study Sponsor, Cheetah Medical.

## 11.3 Site Monitoring

The Sponsor or designee may conduct periodic compliance assessments at various study sites. The Sponsor or designee may request access to all study records including source documentation for inspection and photocopying during a compliance assessment. The Investigator and research coordinator must be available to respond to reasonable requests and queries made during the compliance assessment process.

## 11.4 Regulatory Agency Inspection

In the event that an investigator is contacted by a regulatory agency regarding this study, the investigator will notify the Sponsor or its designee immediately. The investigator and research coordinator must be available to respond to reasonable requests and queries made during the inspection process. The investigator must provide the Sponsor or designee with copies of all correspondence that may affect review of the current trial. The Sponsor may provide needed assistance in responding to regulatory audits.

# 12. STATISTICAL CONSIDERATIONS

## 12.1 Sample Size Estimation

Subjects will be randomly assigned in a 2:1 ratio to treatment with Starling SV or to treatment with standard of care. The primary effectiveness endpoint for this study is the difference between the two treatment groups in mean fluid balance at ICU discharge.

Minimum enrollment ($N_{min}$) in the study will be set at 120 subjects (80 Starling SV and 40 control) to power at 80% for possible demonstration of superiority for the secondary endpoint of creatinine levels as a measurement of change from baseline. The secondary endpoint for change in creatinine levels at 120 evaluable subjects displays 80% power at a two-sided alpha level of

0.05 to demonstrate superiority under an assumption of a treatment effect of -1.4 mg/dL with a standard deviation of 2.5 mg/dL.

Under an assumption of a treatment effect of -2 L with a standard deviation of 3 L, the sample size of 120 evaluable subjects provides 92.7% power in a test of superiority for the primary effectiveness endpoint.

The trial will incorporate a sample size re-estimation (SSR) at the time of the interim look based on promise for superiority in the key secondary endpoint. Methods for the SSR have been described in detail in previous literature. The maximum enrollment being considered for this trial is 210 total enrolled ($N_{max}$ = 1.75 times $N_{min}$).

An interim analysis incorporating a SSR will take place when 120 subjects have been enrolled and completed endpoint evaluations. The interim analysis will be performed by an independent statistician. It is assumed that the acute endpoint assessments will be fully informed at the time of the interim analysis.

At this point, the primary study endpoint will be tested as final, and will not incorporate an alpha spend.
The conditional power to claim superiority ($CP_{sup}$) on the key secondary endpoint for change in creatinine levels will be computed. The conditional power ($CP_{sup}$) will be calculated based on the interim results of the key secondary endpoint, with the specific interest of demonstrating superiority. $CP_{sup}$ is defined as the approach that quantifies the statistical power to yield an answer different from that seen at the interim analysis. The data will be partitioned into three zones based on $CP_{sup}$ unfavorable zone ($CP_{sup}<50\%$), promising zone ($50\%\leq CP_{sup}<80\%$), and favorable zone ($CP_{sup}\geq 80\%$).

## 12.2 Analysis Populations

### *12.2.1 All Enrolled*

Any subject who has signed informed consent will be included in the all enrolled population. Should a subject be considered a screen failure, the reason for failure will be documented, and the subject will be exited from the study. Adverse events will be reported for all enrolled subjects through the time of study exit.

### *12.2.2 Intent-to-Treat (ITT)*

The intent-to-treat population (ITT) will consist of any subjects that have signed the ICF, meet study eligibility criteria, and are randomized to the treatment or control arm of the study.

### *12.2.3 Modified Intent-to-Treat (mITT)*

Subjects will be included in the Modified Intent-to-Treat group if they sign the ICF, meet study eligibility criteria, are randomized, and in the treatment group receive monitoring for the first 72 hours of study enrollment or until ICU discharge, whichever occurs first. The mITT population represents the Primary and Secondary Analysis population for this study.

### *12.2.4 Per-Protocol (PP)*

Subjects will be included in the Per-protocol group if they sign the ICF, are randomized and have the assigned procedure completed, meet critical study eligibility criteria and have no major protocol deviations (defined in the Statistical Analysis Plan), and, in the treatment group, receive monitoring for the first 72 hours of study enrollment. The PP population represents a subgroup analysis population for this study.

## 12.3 Primary Endpoint Analysis

The primary endpoint is an evaluation of the difference between the two treatment groups in mean fluid balance (L) at 72 hours or ICU discharge, whichever occurs first. The following hypothesis will be tested:

$$H_{o:}\ \mu c - \mu_T = 0$$
$$Ha:\ \mu c - \mu_T \neq 0$$

where μt and μc is the average fluid balance in the Starling SV and control groups, respectively. Statistical summaries will include means, medians, and standard deviation, as well as 95% confidence intervals. A t-test for superiority at a significance level of 0.025 will be performed to test the hypothesis that μt is significantly less than μc. If it can be established that the difference is greater than 0 points (i.e. $\mu C > \mu T$), superiority will also be claimed.

## 12.4 Secondary and Exploratory Endpoints

Secondary objectives that have been pre-specified to be included in the formal statistical analysis will be tested in sequential fashion using the Holms step-down procedure for type-I error rate correction if and only if the primary objective passes according to the criteria outlined above. At the conclusion of the trial, the key secondary endpoints will be ordered sequentially from most significant to least significant. The endpoints will then be tested in order at adjusted levels of significance (i.e. E1: 0.05/k, E2: 0.05/k-1; E3: 0.05/k-2, where k=number of specified endpoints). Once an endpoint fails, all following endpoints will not be tested. Following is a list of key secondary endpoints:

Following is a list of key secondary endpoints for formal testing:

- Length of ICU stay (days) until subject is medically ready for discharge
- Number of days free from ventilator use (30 day period)
- Requirement for mechanical ventilation
- Number of days free from vasopressor use
- Changes in serum creatinine levels from baseline
- Requirement for renal replacement therapy (RRT)

Additional secondary endpoint have also been identified for testing, but will not be included in the formal statistical testing procedures for key secondary endpoints:

- Incidence of Adverse Events (AE)

- Number of ICU readmissions
- Mortality rate
- Mean volume of treatment fluid
- Incidence of Major Adverse Cardiac Event (MACE)
- Discharge location
- Mean difference in fluid balance at ICU discharge

Additional sub-analyses have been planned for the primary and key secondary endpoints. Primary and secondary endpoints will also be evaluated by the following subgroup analysis:

- Patient disease state
- Patients determined to be fluid responsive vs non-fluid responsive
- AKI measures in patients determined to increase serum creatinine levels from baseline vs decrease serum creatinine levels from baseline
- Enrollment time frame

### 12.5 Baseline Data Summary

Baseline data including subject demographics, clinical history, risk factors, and pre-procedure patient characteristics will be summarized using descriptive statistics (e.g., mean, median, standard deviation, 25th percentile, 75th percentile, minimum and maximum) for continuous variables and frequency tables or percentages for categorical variables.

### 12.6 Subject Accountability and Missing Data

Subjects enrolled in this study are followed for a short time period, and missing data in this study is expected to occur at a low rate. All efforts will be used to prevent missing data. These efforts include, but are not limited to, complete site training and regular monitoring to help to minimize missing data.

Subjects without the minimum amount of monitoring [i.e. throughout first 72 hours of study enrollment,] and measurements specified in the protocol will be considered as missing in the final analysis. The impact of missing data on the study will be evaluated via sensitivity analyses if more than 5% of subjects do not have evaluable data for the primary outcome. In the final report, the number and proportion of subjects eligible for and compliant with each analysis population will be presented.

## 13. DATA HANDLING AND RECORD KEEPING

Each participating site will maintain appropriate medical and research records for this trial, in compliance with regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a manufacturer-sponsored study, each site will permit authorized representatives of the Sponsor(s), the Sponsor's designee, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the trial.

## 13.1 Clinical Data Collection

Electronic Case Report Forms (eCRFs) will be used to collect all subject data during the course of the study and will be entered into an electronic database. eCRFs must be fully completed for each subject and signed by the Investigator when complete.

Good Clinical Practice Guidelines require that Investigators maintain information in the study subject's medical records that corroborate data collected on the eCRFs. In order to comply with these regulatory requirements, the following information should be maintained:

- Medical history/physical condition of the study subject before involvement in the study sufficient to verify protocol entry criteria.
- Dated and signed notes on the day of entry into the study including the study investigator, study name, subject number assigned and a statement that consent was obtained.
- Dated and signed notes from each study subject visit with reference to the eCRFs for further information, if appropriate (for specific results of procedures and exams).
- Information related to adverse events.
- Study subject's condition upon completion of or withdrawal from the study.
- Discharge summaries/procedure reports.

## 13.2 Data Reporting

All site Investigators or designated individuals shall be responsible for recording all study data on the eCRFs. The Investigator is required to electronically sign the eCRFs to verify that he/she has reviewed and agrees with the recorded data. All protocol deviations shall be documented and a justification for any missed assessments shall be provided on the Protocol Deviation eCRF.

Completed eCRFs will be verified by the monitor at the investigational sites or by remote monitoring as at regular intervals throughout the study, as outlined in the Monitoring Plan. The Investigator will allow the monitor and/or representative of the Sponsor, and any regulatory body to review and inspect the study files, subject eCRFs, subject medical records and other related study documents as required.

## 13.3 Data Review

eCRFs will be reviewed for completeness and clarity. Missing or unclear data will be investigated by the monitor and will be retrieved, clarified and entered by study personnel as necessary throughout the study. Cheetah Medical, or designee, may request additional documentation from the Investigator such as physician notes or physician written summaries when adverse events are observed and reported. Documentation provided will also be used for the adjudication of specified adverse events by the Independent Safety Physician.

Development of the data collection system for the study will be performed by Cheetah Medical, or designee. Cheetah Medical, or designee will also be responsible for the quality control of the database and confirming the overall integrity of the data.

## 13.4 Investigator Records

Investigators will maintain complete, accurate and current study records. The following records must be maintained in designated study files:

- Clinical protocol and all amendments
- Signed Clinical Trial Research Agreement
- Institutional Review Board (IRB) Approval Letter(s)
- IRB approved informed consent(s) (including any revisions)
- CV for all Investigators, signed and dated
- Investigator(s) medical license
- Financial Disclosure Form for all Investigators
- Correspondence relating to this study
- Correspondence with the IRB
- IRB membership list and/or assurance number
- Delegation of Authority log
- Device Instructions for Use
- Printed copy of blank set of CRFs
- Subject Log
- Site Visit Log (e.g. for Monitor sign-in)
- Site Training records
- Investigational Device Accountability Logs
- Reports (includes Adverse Event reports and final reports from Investigator and Sponsor)
- Copy of all IRB approved subject-related materials and/or study advertising materials

The following records must be maintained for each subject enrolled in the study:

- Signed subject consent forms
- Copy of final completed CRFs
- Record of any adverse events with supporting documentation
- Reports, progress notes, physician and/or nursing notes, and subject office files
- Records pertaining to subject deaths throughout the course of the study

### 13.5 Data Retention

Study documents should be retained for a minimum of 5 years. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

**Table 2: Responsibilities for Preparing and Submitting Reports**

| Type of Report | Prepared by Investigator for | Time of Notification |
|---|---|---|
| Enrollment Notification Form | Sponsor | Within 24 hours of procedure |
| Electronic Case Report Forms | Sponsor | Within 10 working days |
| Serious/ Device Related Adverse Event | Sponsor and IRB (as required) | Within 24 hours of knowledge or as required by IRB |
| Subject Death | Sponsor and IRB (as required) | Within 24 hours of knowledge |
| Subject Withdrawal | Sponsor | Within 24 hours of knowledge |
| Withdrawal of IRB Approval | Sponsor | Within 24 hours of knowledge |
| Protocol Deviations | Sponsor and IRB | Within 5 working days of occurrence or knowledge |
| Informed Consent Not Obtained | Sponsor and IRB | Within 24 hours of knowledge or as required by IRB |
| Final summary report | Sponsor and IRB and Regulatory Authority (as required) | Within 3 months of study completion |

### 13.6 Investigator Reports

Each year an annual summary report shall be prepared by the Investigator which provides a summary of the number of subjects treated to date as well as other pertinent clinical information associated with the investigational procedure. The annual report is required to be provided to the IRB and the Sponsor or designee.

Upon completion and/or termination of the study a final report shall be prepared. This report will contain a critical evaluation of all data collected during the course of the investigation at each institution. The Sponsor or its designee is responsible for preparing this compilation to Investigators for submittal as a final report to their reviewing IRB.

## 14. QUALITY CONTROL AND ASSURANCE

### 14.1 Site and Investigator Selection

The Sponsor selects qualified investigators with appropriate experience with this patient population at health care facilities with adequate resources to participate in this study. Investigational sites will be selected using combined current assessments of site and investigator qualifications.

### 14.2 Protocol Deviations

An investigator is not allowed to deviate from the Protocol if the deviation affects subject's rights, safety and wellbeing, or the scientific integrity of the clinical investigation. Under

emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Sponsor and the IRB.

A protocol deviation is a failure to comply with the requirements specified within this clinical study protocol. Examples of protocol deviations may include enrollment of a study subject who does not meet all of the inclusion/exclusion criteria specified in the protocol and missed study visits without documentation. Each investigator shall conduct this clinical study in accordance with this clinical study protocol, regulatory body regulations, Good Clinical Practices.

All deviations are reviewed and assessed for their impact on subject safety by the Sponsor or designee. The PI and study staff is responsible for knowing and adhering to their IRB reporting requirements.

The protocol deviations for this protocol consist of, but not limited to the following:

- Failure to obtain subject's informed consent prior to any study-related activities;
- Subject did not meet the inclusion and/or exclusion criteria and were enrolled;
- Failure to conduct protocol required clinical test or assessment;
- Failure to complete protocol required assessments within the required time frame
- Failure to report serious adverse events according to protocol requirements.

In the event of any deviation from the protocol, the Investigator will be notified of the site's non-compliance. Corrective actions will be required, if necessary. Continued protocol deviations despite re-education of the study site personnel or persistent protocol deviation may result in termination of the site's study participation. Subjects enrolled at these sites will continue to be followed per the clinical protocol.

### *14.2.1 Protocol Deviation Process*

Investigators must report protocol deviations to the Sponsor within 5 working days of investigational site knowledge of the deviation by entering data into the eCRF. Any protocol deviations that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances must be reported within 24 hours to the Sponsor and IRB, if required by the IRB, or national regulations.

## 14.3 Corrective/Preventive Action

Deviations from clinical protocol requirements will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective actions will be put into place to bring a site into compliance.

## 14.4 Study Audit(s)

Audits may be performed as deemed necessary by Cheetah Medical, in a manner consistent with applicable procedure.

## 14.5 Study Registration

A description of this trial will be available on www.clinicaltrials.gov, the U.S. approved clinical trial registry site.

# 15. ETHICS/PROTECTION OF HUMAN SUBJECTS

## 15.1 Statements of Compliance

This study will be performed in accordance with Good Clinical Practice Guidelines, the Code of Federal Regulations Title 21 CFR Parts 50, 54, and 56.

The clinical investigation shall not begin until the required approval/favorable opinion from the Institutional Review Board (IRB) has been obtained including approval of the Informed Consent Form to be used with subjects.

Any additional requirements imposed by the IRB shall be followed.

## 15.2 Institutional Review Board

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents by an appropriate Institutional Review Board (IRB) prior to subject enrollment. Any amendments to the protocol or changes to the informed consent document must also be approved before they are placed into use. The Investigator should notify the IRB of deviations from the protocol and SAEs occurring at the site in accordance with local procedures. The Investigator is responsible for continued study related communication with the IRB, including submission of study report and SAE notifications as per local regulatory requirements.

## 15.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects (and their families, as applicable). Consent forms describing in detail the study interventions/ products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting any study-specific tests or intervention /administering of study product.

Consent forms will be approved by the IRB and the subject will be asked to read and review the document. Upon reviewing the document, the site investigator or designated study personnel will explain the research study to the subject and answer any questions that may arise. The subject (or their authorized legal representative) will sign the informed consent document prior to any procedures being done specifically for the study. The subject should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate, unless study timeframes do not allow for such discussions. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Modifications to the study informed consent must have approval from the Sponsor and the EC as required.

### 15.4 Subject Confidentiality

Confidentiality of data shall be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. Sites will maintain subject privacy in accordance with local and national regulations and institutional requirements including all applicable provisions of the Health Insurance Portability and Accountability Act (HIPAA) and its current regulations.

Subjects must be identified only by their assigned study number and initials on all CRFs and other records and documents submitted to the Sponsor, the monitor, and other authorized parties. The Investigator should maintain a Subject Identification List with complete identification information (name, address, contact number, informed consent version number) on each subject. Documents not required to be submitted to the Sponsor such as subject written informed consent form, should be maintained by the Investigator in strict confidence.

The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. The principal investigator or institution shall provide direct access to source data during and after the clinical investigation for monitoring, audits, IRB review and regulatory authority inspections. As required, the principal investigator or institution shall obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical investigation.

## 16. PROTOCOL AMENDMENTS

The clinical protocol, eCRFs, ICF and other subject information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. Proposed amendments to the protocol shall be agreed upon between the Sponsor and Principal Investigator, or the Coordinating Investigator. The amendments to the protocol and the subject's informed consent form shall be notified to, or approved by, the IRB as required. For non-substantial changes [e.g. minor logistical or administrative changes, change of monitor(s), telephone numbers, renewal of insurance] not affecting the rights, safety and well-being of human subjects or not related to the clinical investigation objectives or endpoints, a simple notification to the IRB can be sufficient. The version number and date of amendments shall be documented.

## 17. TERMINATION OF STUDY OR STUDY SITE PARTICIPATION

The Sponsor may terminate the study at any time. If the study is terminated prior to the completion of expected enrollment for any reason, all participating centers will be notified within five working days. All subjects already enrolled will continue to be followed for the planned course of study described in this protocol. The study shall be terminated following the last enrolled subject.

The Sponsor reserves the right to terminate study site participation and remove appropriate study materials at any time. Specific instances that may precipitate such termination include but are not limited to the following:

- Failure to meet minimum subject enrollment requirements
- Failure to comply with protocol specified procedures and documentation
- Failure to comply with regulatory regulations
- Failure to comply with Good Clinical Practice

The site Investigator may also discontinue study participation with suitable written notice to the Sponsor.

## 18. PUBLICATION POLICY

Specifics of the publication policy will be outlined in the Clinical Trial Research Agreement.

## 19. BIBLIOGRAPHY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## APPENDIX A- TREATMENT ALGORITHM