CLINICAL PROTOCOL

A CLINICAL STUDY TO EVALUATE THE SAFETY AND ACCURACY OF THE SARANAS EARLY BIRD™ BLEED MONITORING SYSTEM FOR THE DETECTION OF ENDOVASCULAR PROCEDURE RELATED BLEEDING EVENTS

Protocol Number: PVP004

Original Protocol Issue Date: May 4, 2018

Sponsor:

Saranas, Inc.
2450 Holcombe Blvd
Houston TX 77021
Tel: (713) 357-1049

CONFIDENTIALITY STATEMENT

STUDY SYNOPSIS

Title	A Clinical Study to Evaluate the Safety and Accuracy of the Saranas Early Bird Bleed Monitoring System for the Detection of Endovascular Procedure Related Bleeding Events
Protocol Number	PVP004
Investigational Product	Saranas Early Bird Bleed Monitoring System (EBBMS)
Subject Population	Patients undergoing a large-bore (≥10F) endovascular procedure via femoral access
Study Objectives	To evaluate the safety and accuracy of the Saranas EBBMS for the detection of access site related internal bleeding events during large-bore endovascular procedures
Primary Endpoint	Level of agreement in bleeding detection between the Saranas EBBMS and post-procedural computerized tomography
Secondary Endpoints	• Level of agreement in bleeding detection between the Saranas EBBMS and clinical assessment or post-procedural computerized tomography • Device sensitivity in bleeding detection of the Saranas EBBMS as compared to post-procedural computerized tomography • Device specificity in bleeding detection of the Saranas EBBMS as compared to post-procedural computerized tomography • Device sensitivity in bleeding detection between Saranas EBBMS and clinical assessment or post-procedural computerized tomography • Device specificity in bleeding detection between Saranas EBBMS and clinical assessment or post-procedural computerized tomography • Relationship between level (severity) of bleed detected by the Saranas EBBMS and the severity of bleeding as assessed by computerized tomography • Relationship between level (severity) of bleed detected by the Saranas EBBMS and the severity of bleeding as assessed by the absolute drop in hemoglobin • Relationship between level (severity) of bleed detected by the Saranas EBBMS and the number of transfusions • Relationship between level (severity) of bleed detected by the Saranas EBBMS and the severity of bleeding as assessed by

	VARC-2 criteria • Relationship between level (severity) of bleed detected by the Saranas EBBMS and the occurrence of post-procedural acute kidney injury
Safety Endpoints	From enrollment until end of study, all: • Device and procedure-related adverse events • Serious adverse events • Serious adverse device effects
Study Design	This is a multi-center, open-label study to evaluate use of the Saranas EBBMS for detection of access site-related internal bleeding events during large-bore endovascular procedures. After signing consent, subjects will undergo screening procedures and be scheduled for their endovascular procedure. The endovascular procedure will be performed per the institution's standard practices, with inclusion of monitoring using the Saranas EBBMS. Following completion of the procedure, subjects will continue to be monitored using the Saranas EBBMS for internal bleeds for up to 8 hours. The Saranas EBBMS will then be removed. Adverse events and device effects will be recorded from enrollment of subjects and throughout the procedure, until discharge of subjects.
Study Procedures	After signing Informed Consent, subjects will undergo screening procedures including assessment of eligibility, demographics, medical history, concomitant medications, physical examination, indication for intervention, and laboratory assessments. Following confirmation of eligibility and enrollment, subjects will optimally undergo a CT scan (with or without contrast; not mandatory) prior to the endovascular procedure to assess for the presence of prior recent bleeding events or vascular complications. They will then undergo their planned endovascular procedure with monitoring for internal bleeding using the Saranas EBBMS. Following completion of the endovascular procedure, subjects will undergo non-contrast CT to detect or confirm internal bleeding, if medically possible. Subjects will continue Saranas EBBMS monitoring for up to 8 hours after completion of the endovascular procedure.
Number of Patients:	100
Number of Sites	5-10 sites in the US

Study Duration	The study is anticipated to be approximately 5 months in duration. The duration of each subject's participation will be approximately 1 day.
Inclusion Criteria	• ≥18 years of age • Willing and capable to sign an Informed Consent form • Planned large-bore endovascular procedure via the common femoral artery using a large bore catheter (≥10 Fr) such as trans-femoral transcatheter aortic valve replacement (TAVR), balloon aortic valvuloplasty, complex or high-risk percutaneous coronary intervention requiring hemodynamic support device (Impella 2.5, Impella CP, and ECMO), or endovascular aortic repair (EVAR).
Exclusion Criteria	• Subject is participating, or planning to participate in a clinical trial or study of an investigational product that may influence the data collected for this investigation • Inability to access common femoral artery or vein with large bore catheters • Unstable conditions such as cardiogenic shock, or ST-elevated MI • Current active bleeding • Pre-procedural conditions precluding the realization of a post-procedural CT scan • Pregnancy • Mental disability or any other lack of fitness, in the Investigator's opinion, to preclude subject's participation in or ability to complete the study as planned.
Statistical Methods	Descriptive statistics to be reported for each analyzed variable will include the number of observations, mean, median, standard deviation and range for quantitative variables, frequency and relative percent for ordinal and categorical variables. Level of agreement will be assessed using Cohen Kappa statistic for categorical variable, intraclass correlation for multiples categories, and Pearson correlation for continuous variables. Summary statistics will be displayed in tabular and/or graphical format. Missing data will not be interpolated for any analyses. Any hypothesis tests will be performed using a two-sided significance level of 0.05.

Table 1. Schedule of Events

Procedure/ Assessment	**Screening** -14 to 0 days	**Day of Procedure**			
		Prior to large bore sheath Insertion	During procedure	Post-procedure	At discharge
Informed consent	X				
Eligibility	X				
Demographics	X				
Medical history/indication	X				
Concomitant medications	X				
Physical exam	X				
Serum CBC/Creatinine/PT-PTT/INR	X	X[1]		X[2]	X
Activated clotting time			X	X[2]	
Large bore endovascular access plan		X			
Contrast CT scan	X[3]				
Non-contrast CT scan	X[3]			X	
Saranas EBBMS insertion		X			
Saranas EBBMS monitoring			X[4]	X[4]	
Saranas EBBMS removal				X	
Adverse events		X	X	X	

1. Just after Saranas EBBMS insertion and before its activation
2. Immediately before Saranas EBBMS removal
3. If available per standard of care. May be performed up to 90 days prior to the procedure.
4. For up to 8 hours following procedure

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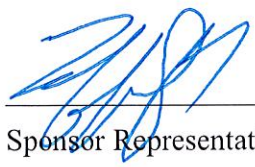
PROTOCOL NUMBER: PVP004

PROTOCOL APPROVALS



Sponsor Representative

May 4, 2018

Date

_____ _____

Date

INVESTIGATOR APPROVAL

I have read and familiarized myself with this protocol and I agree to conduct the study as described.

_____ _____

Principal Investigator Date

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LIST OF ABBREVIATIONS

ADE	Adverse device effect
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CBC	Complete blood count
CFA	Common femoral artery
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computed Tomography
DC	Device complication
EBBMS	Early Bird Bleed Monitoring System
ECMO	Extra corporeal membrane oxygenation
EVAR	Endovascular aortic repair
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GRACE	Global Registry of Acute Coronary Events
IBC	Internal bleeding complications
IDE	investigational device exemption
IFU	Instructions for use
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
MI	Myocardial infarct
NHLBI	National Heart and Lung Association
PCBA	Printed circuit board assembly
PP	Per protocol
PT	Prothrombin time
PTT	Partial thromboplastin time
SAE	Serious adverse event
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum glutamic pyruvic transaminase
TAVR	Trans-femoral aortic valve replacement
TIMI	Thrombolysis in myocardial infarction
UADE	Unanticipated adverse device effect
UID	User interface display
VARC	Valve Academic Research Consortium

1.0 INTRODUCTION

1.1 Background

Vascular access is necessary for any medical procedure that requires stable communication with a blood vessel. In 2010, more than 17 million procedures requiring vascular access were performed in the United States[1,2]. One percent of these procedures were associated with a bleeding complication at the access site severe enough to warrant blood transfusion. These complications are difficult to detect; in most cases, extensive bleeding has occurred by the time signs or symptoms become evident.

Vascular access is most commonly achieved by using a hollow-bore needle to puncture the vessel, then introducing a hollow sheath into the vessel via the Seldinger technique[3]. The sheath provides the operator with a stable means of introducing and removing devices such as balloons and stents (in cardiac, vascular, or interventional radiology procedures), infusing medications (in chronic chemotherapy or antibiotic therapy), filtering blood (in hemodialysis), or removing blood for analysis (in the assessment of hospitalized patients, especially those who are critically ill).

The single most frequent complication associated with any procedure involving vascular access is an internal bleeding complication (IBC) at the site where the needle initially enters the blood vessel[4,5]. Often, during initial vessel puncture, the physician may accidentally penetrate the wall of the vessel, initiating an IBC. Bleeding is further aggravated by the fact that patients undergoing these procedures are often receiving high-dose of anticoagulant therapy.

In a recent review, Vavalle and Rao summarized key studies and registry data involving IBC's in patients undergoing percutaneous coronary interventions and showed that any degree of procedural bleeding is associated with significantly increased risk of ischemic injury and mortality[6]. In a three-hospital registry (n=10,974) described by Kinnaird et al, 5.4% of the patients had major bleeding (Thrombolysis in Myocardial Infarction [TIMI] classification) and received transfusions. In the National Heart Lung and Blood Association (NHLBI) registry (n=6,656), 1.8% of the patients had access site hematomas that necessitated transfusion[7]. In the Global Registry of Acute Coronary Events (GRACE) (n=24,045), there was a 3.9% incidence of major bleeding; almost a fourth of these hemorrhages (23.8%) occurred at the vascular access site[8,9].

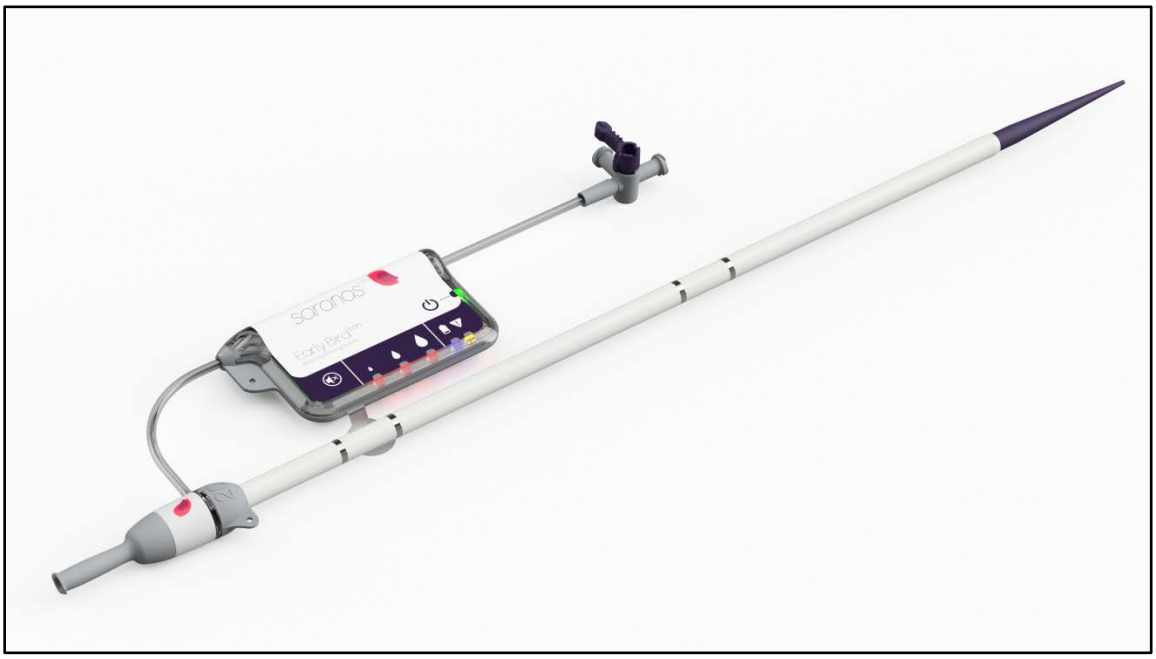
Many IBC's are noted only after sheath removal. However, their trigger is thought to occur at the time of needle puncture, and small leaks are believed to occur before and during sheath placement. Early awareness of internal bleeding will allow physicians to directly and immediately address this complication and increase post-procedural vigilance in these vascular interventions[10,11].

In most cases, extensive bleeding has invariably occurred when signs or symptoms become evident[12,13]. This often necessitates surgical intervention and/or blood transfusions to manage these complications. Bleeding at the vascular access site is associated with increased mortality, length of hospitalization and cost[8,14,15].

Presently, no marketed technology exists that can alert clinicians to an ongoing IBC immediately at its onset during a vascular access procedure. Although existing imaging

modalities such as ultrasound and computed tomography (CT) scans can identify these bleeding complications, it would be impractical and expensive to prophylactically incorporate their use as part of the clinical workflow for every procedure involving vascular access. To address this unmet need, Saranas has developed the Early Bird Bleed Monitoring System, hereinafter referred to as Saranas EBBMS (**Figure 1**), to detect an IBC in real-time without interrupting normal procedures. This technology may enable physicians to mitigate downstream consequences by addressing these complications immediately, thereby lowering long-term risks to the patient and the associated healthcare expenditures.

Figure 1 Saranas Early Bird Bleed Monitoring System



1.2 Report of Prior Investigations

1.2.1 Animal Investigations

In addition to the prospective, self-controlled acute animal investigation described below, at least three earlier prototype iterations of the Saranas EBBMS (>30 devices) were tested in swine and ovine animal models. The results from earlier studies provided evidence that a functionalized vascular access sheath using bioimpedance spectroscopy can detect an intraprocedural vascular access IBC through measuring significant changes in normalized bioimpedance response curves. These results concluded that the Early Bird device design was final and ready for validation. Also, completion of these earlier studies enabled refinement of the validation protocol and study design.

Prospective Animal Investigation Summary

A prospective, self-controlled acute animal investigation was conducted to evaluate the safety and efficacy of the Saranas EBBMS in detecting extravascular fluid accumulation via simulated IBC. The primary endpoint was sensitivity of level 1 bleed detection, and the secondary

endpoint was bleed progression performance. Additional endpoints were histology, local tissue and systemic response, overall animal health and device handling characteristics.

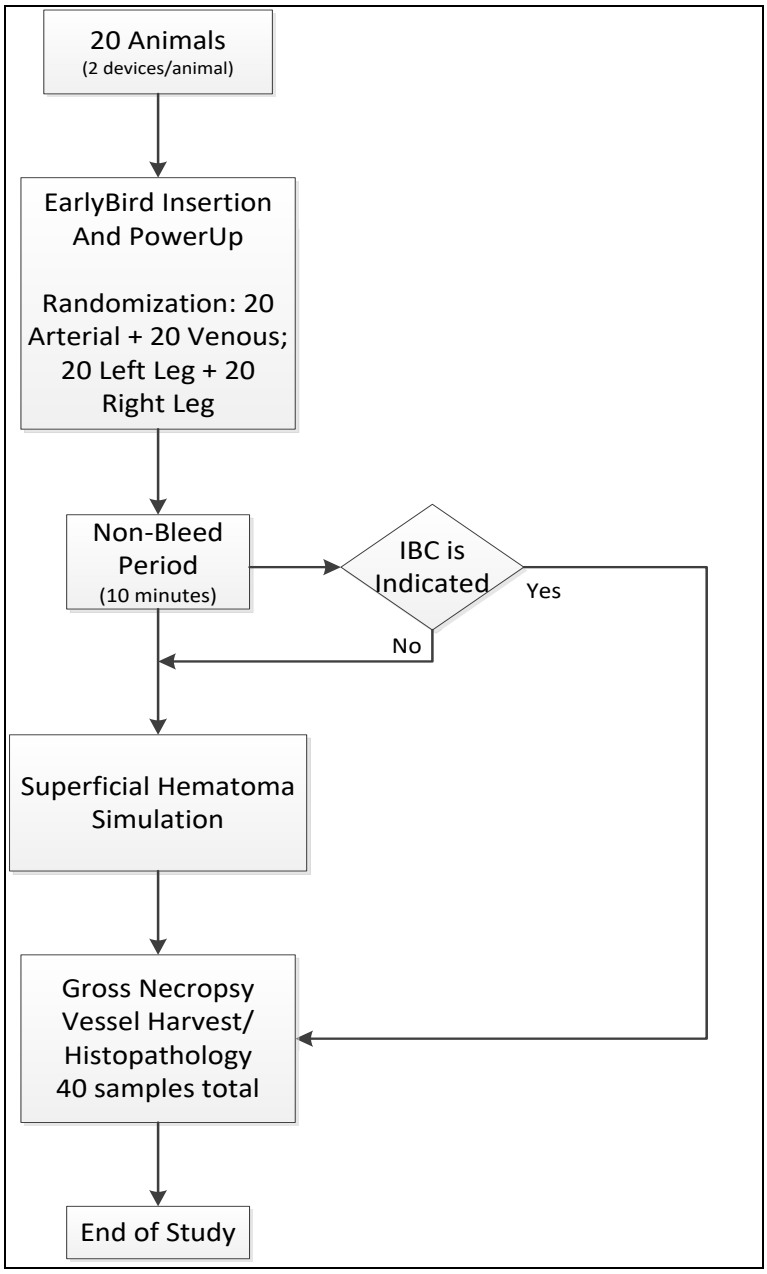
Test Animals

Test animals were 20 female Yorkshire Cross swine > 70kg. Swine were selected as the vasculature is similar to humans with respect to blood pressure and blood flow in the femoral arteries and veins, and clinical bleeding simulations can be reasonably well carried out with injection volumes that are deemed critical in human interventions.

Procedure

Two legs were used on each animal, with the sequence of testing of the left and right legs and use of an artery or vein being randomized. The study flow chart is shown in **Figure 2**.

Figure 2 Animal Study Flow Chart



After anesthesia and preparation of the insertion site, the Saranas EBBMS was introduced into the artery or vein, and a clinical intervention was simulated (non-bleed phase). For the bleed simulation phase, blood solution injection was initiated with a peristaltic pump to infuse 500 mL of blood solution at a rate of 10mL/min, into the treatment site with clinical interventions simulated. Once Saranas EBBMS blood level indicators (1, 2 and 3) were triggered, infused volumes and fluoroscopic images were collected. Animals were then euthanized.

Each animal was observed during the test period, and any abnormal findings were recorded including local, systemic and behavioral abnormalities and their potential influence on the results

obtained in the study outcomes. All observed instances of animal illness and death were recorded during the study.

Results and Conclusions

The outcome of the study resulted in 100% sensitivity and 100% specificity in 40 bioimpedance datasets which included 10 detections of true positive bleeding events (i.e. access site bleeds that occur during the Non-Bleed Phase).

Table 2. Sensitivity and Specificity at Level 1 Detection

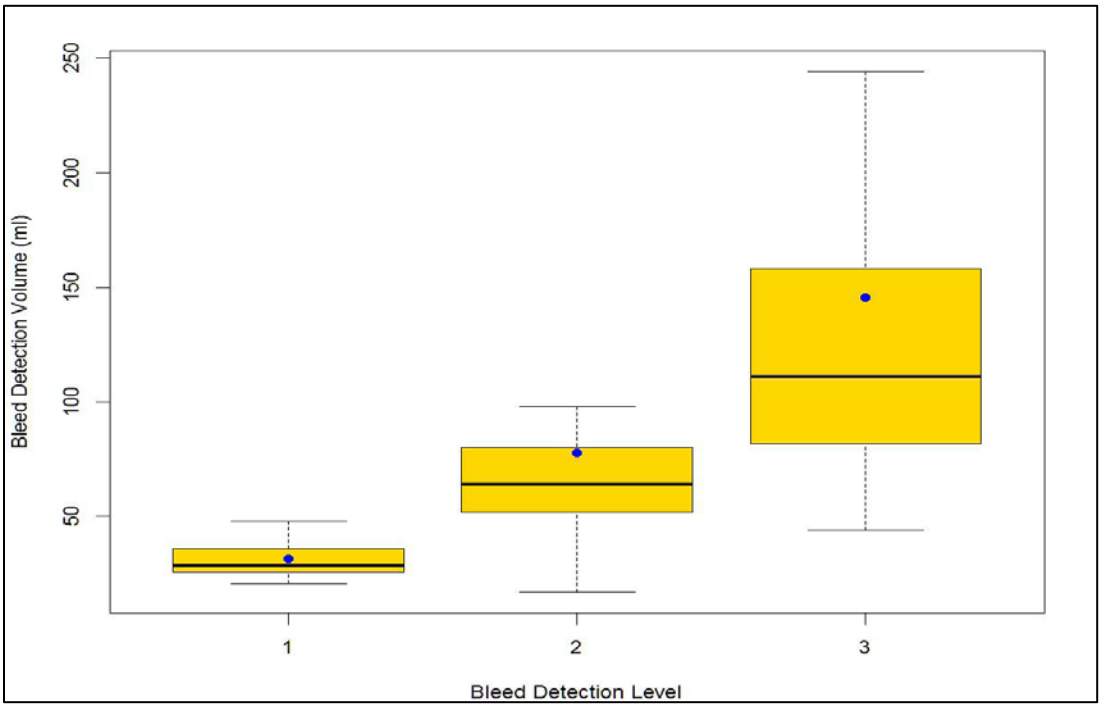
Early Bird Level 1 Bleed Detection	**Bleed Status**	
	Bleed Simulations or Access Site Bleeds	**No Bleed Simulations or No Access Site Bleeds**
Detection	40 = True Positive*	0 = False Positive
Non-Detection	0 = False Negative	30 = True Negative
Sensitivity/Specificity	**Sensitivity = 100%**	**Specificity = 100%**

* 10 bleeds that occurred during the Non-Bleed Phase and 30 bleeds that were detected during the Bleed Simulation Phase (40 total)

Histopathology analysis determined that there was no specific damage to the vessel walls that was associated with the Saranas EEBMS use. Any endothelial loss was attributed to a common outcome of using intravascular devices, and the pathologist noted that the endothelium will reendothelialize within a few weeks with no further damage. All animals survived to the conclusion of their acute implant procedures with no major adverse events noted.

From the 30 simulated IBCs, bioimpedance data were analyzed for volumetric distribution relative to the triggered bleed indicator levels (Levels 1, 2, and 3). Both central tendency statistics (mean, median) and variability statistics (standard deviation, range) increased as the bleed indicator levels increased. There was definitive separation between the distributions at the three bleed indicator levels.

Figure 3. Bleed Detection Volumes



Box and Whisker Plot Depicting Bleed Detection Volumes (mL) at each Bleed Detection Level. The bottom of each box represents the lower quartile (Q_1, the 25th percentile); the top of each box represents the upper quartile (Q_3, 75 percentile), the thick line in each box represents the median (M, the 50th percentile); the "whiskers" represent the farthest points that are not outliers, i.e., that are within 1.5 times the interquartile range of Q_1 and Q_3. The blue dot represents the mean bleed detection volume.

Table 3. Paired Differences Between Bleed Indication Levels

Descriptive Statistics	**Level 2 vs. Level 1**	**Level 3 vs. Level 2**	**Level 3 vs. Level 1**
Mean (SD)	46.3 (46.5)	67.7 (77.2)	114.0 (96.1)
Range	12.0 – 262.0	15.0 – 412.0	38.0 – 461.0
Median	33.5	44.0	81.0
Wilcoxon Signed Rank Test (P-Value)	<0.001	<0.001	<0.001

1.2.2 Human Investigations

To date there have been no investigations in humans.

2.0 STUDY DEVICE

2.1 Intended Use

The Saranas EBBMS is intended:

- to be inserted in the vasculature to provide a conduit for the insertion of endovascular devices while minimizing blood loss associated with such insertions.
- to provide physicians with an early indication of extravascular fluid accumulation, which may be due to a potential internal bleeding complication.
- to detect and monitor changes in bioimpedance due to extravascular fluid accumulation, and to provide physicians with indications that a potential internal bleeding complication is progressing.

2.2 Device Description

The Saranas EBBMS is a standard introducer sheath with a real-time IBC detection system and is designed to integrate smoothly into normal vascular access procedures and/or surgical protocols by continuously sensing and measuring potential changes in regional bioimpedance, which indicate a potential IBC**.** Referring to **Figure 1**, the system consists of the following: a vascular access sheath with 4 embedded electrodes, positioned along the length of the cannula, that form a bioimpedance measurement circuit; a User Interface Display (UID) which houses a printed circuit board assembly (PCBA) running an algorithm that analyzes bioimpedance and can trigger visible and audible indicators to communicate the state of change in bioimpedance, as depicted by the larger blood drop symbols, to the attending physician.

After Saranas EBBMS insertion, baseline bioimpedance readings are collected. As the procedure progresses, the bioimpedance changes in response to an IBC, which is detected by the device. The UID features a three-level bleed indicator system that sequentially illuminates LED indicators to show an increase in IBC progression at the following levels:

- Level 1 indicator (1st LED) is triggered by the early onset of a bleed. An audible alert is momentarily activated once this level is triggered.
- Level 2 indicator (2nd LED) is triggered as the bleed progresses when a bioimpedance threshold is reached. An audible alert, longer in duration than the 1st LED, is momentarily activated once this level is triggered.
- Level 3 indicator (3rd LED) is triggered as the bleed continues to progress further when a higher bioimpedance threshold is reached. An audible alert is activated once this level is triggered and requires the attending physician to silence the device by pressing the silence button.

2.3 Instructions for Use

The Instructions for Use are provided in Appendix B.

2.4 How Supplied

The Saranas EBBMS is supplied sterile and non-pyrogenic, packaged for single use. The package includes a dilator.

2.5 Labeling

The labelling of the product is shown in **Figure 1** below.

Figure 4. Saranas Early Bird Bleed Monitoring System Label

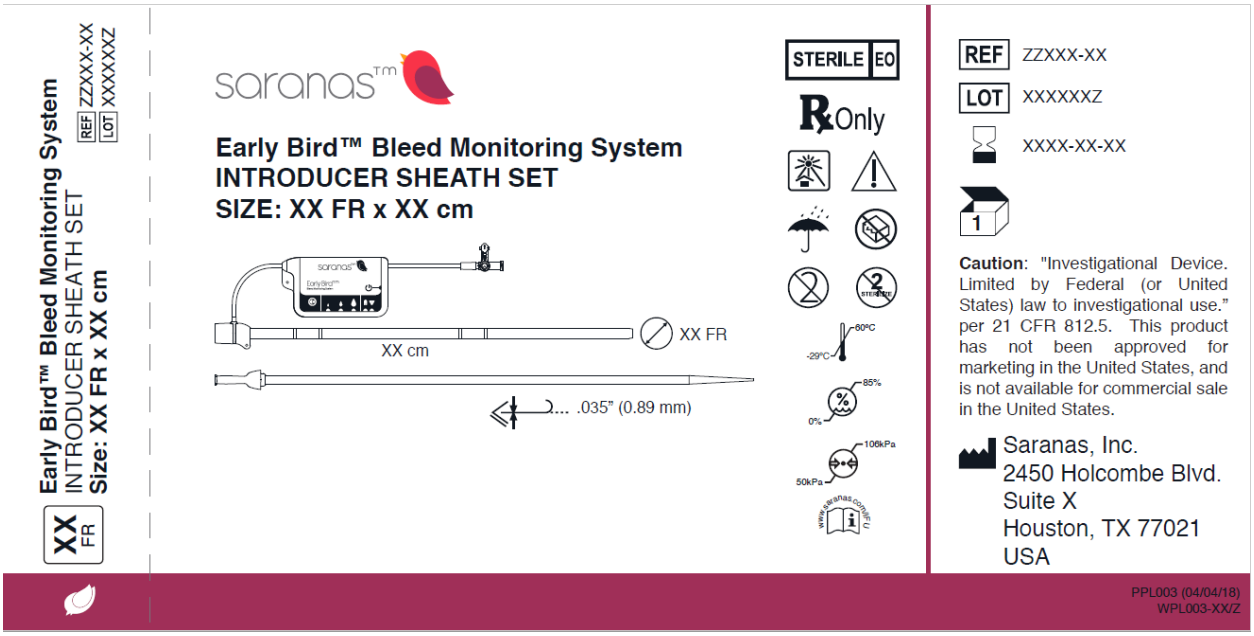


Figure 5. User Interface Display Label

The label shown in **Figure 5** will also have a (handwritten) 3-digit number to identify each individual device.

2.6 Device Storage

Store in a cool, dry place.

3.0 DESIGN OF THE STUDY

3.1 Objectives

The objectives of this study are to assess the preliminary safety and efficacy of the Saranas EBBMS for the detection of access site related internal bleeding events during endovascular procedures.

In addition, device usability, access site bleed rates and vascular complication rates will be assessed.

3.2 Endpoints

3.2.1 Primary Endpoint

The primary endpoint is the level of agreement in bleeding detection between the Saranas EBBMS and post-procedural computerized tomography.

3.2.2 Secondary Endpoints

The following secondary endpoints will be assessed:

- Level of agreement in bleeding detection between the Saranas EBBMS and clinical assessment or post-procedural computerized tomography.
- Device sensitivity in bleeding detection of the Saranas EBBMS as compared to post-procedural computerized tomography.
- Device specificity in bleeding detection of the Saranas EBBMS as compared to post-procedural computerized tomography.
- Device sensitivity in bleeding detection between Saranas EBBMS and clinical assessment or post-procedural computerized tomography.
- Device specificity in bleeding detection between Saranas EBBMS and clinical assessment or post-procedural computerized tomography.
- Relationship between level (severity) of bleed detected by the Saranas EBBMS and the severity of bleeding as assessed by computerized tomography.
- Relationship between level (severity) of bleed detected by the Saranas EBBMS and the severity of bleeding as assessed by the absolute drop in hemoglobin.
- Relationship between level (severity) of bleed detected by the Saranas EBBMS and the number of transfusions.
- Relationship between level (severity) of bleed detected by the Saranas EBBMS and the severity of bleeding as assessed by VARC-2 criteria.
- Relationship between level (severity) of bleed detected by the Saranas EBBMS and the occurrence of post-procedural acute kidney injury.

3.2.2 Safety Endpoints

From enrollment until end of study, all:

- Device and procedure-related adverse events
- Serious adverse events
- Serious adverse device effects

3.3 Patient Eligibility

3.3.1 Inclusion Criteria

Patients must meet the following inclusion criteria to be eligible for the study:

- ≥18 years of age
- Willing and capable to sign an Informed Consent form
- Planned large-bore endovascular procedure via the common femoral artery using a large bore catheter (≥10 Fr) such as trans-femoral transcatheter aortic valve replacement (TAVR), balloon aortic valvuloplasty, complex or high-risk percutaneous coronary intervention requiring hemodynamic support device (Impella 2.5, Impella CP, and ECMO), and endovascular aortic repair (EVAR).

3.3.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

- Subject is participating, or planning to participate in a clinical trial or study of an investigational product that may influence the data collected for this investigation
- Inability to access common femoral artery or vein with large bore catheters
- Unstable conditions such as cardiogenic shock, or ST-elevated MI
- Current active bleeding
- Pre-procedural conditions precluding the realization of a post-procedural CT scan
- Pregnancy
- Mental disability or any other lack of fitness, in the Investigator's opinion, to preclude subject's participation in or ability to complete the study as planned.

3.4 Subject Withdrawal Criteria

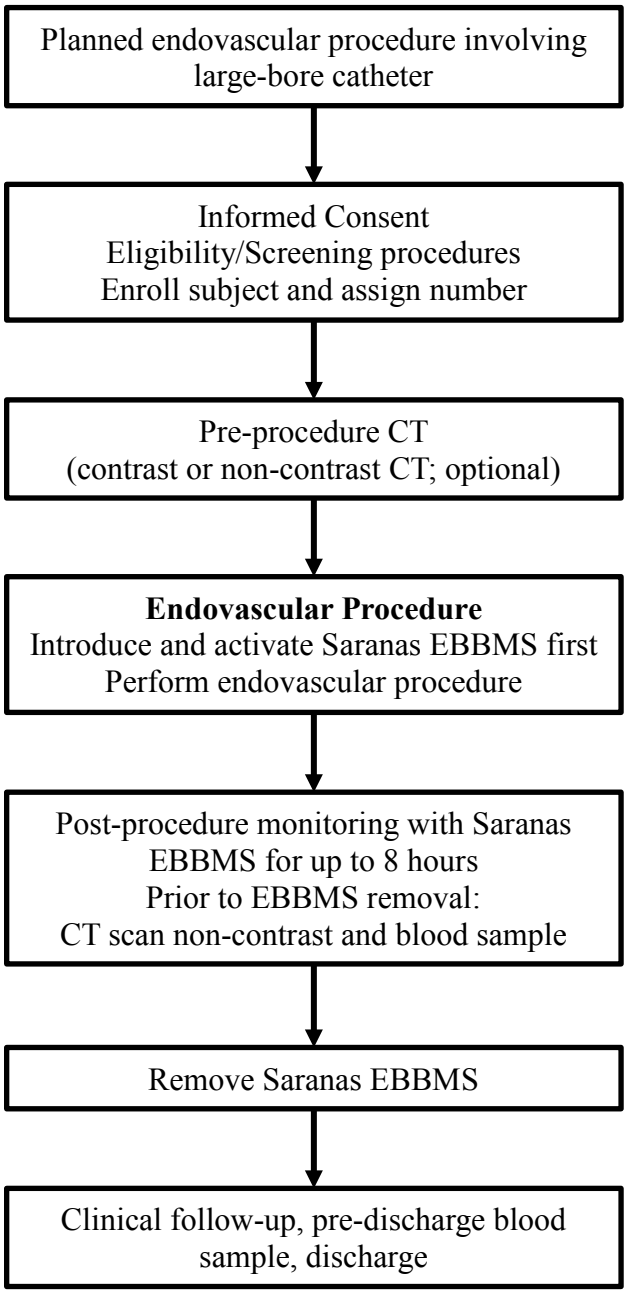
There are no foreseeable situations where subject withdrawal should be required. Withdrawal of a subject from the study will be at the Investigator’s discretion with consideration of the safety and well-being of the subject.

3.5 Study Design

This is a multi-center, open-label study to evaluate use of the Saranas EBBMS for detection of access site-related internal bleeding events during large-bore endovascular procedures.

After signing consent subjects will undergo screening procedures and be scheduled for their endovascular procedure. The endovascular procedure will be performed per the institution's standard practices, with inclusion of monitoring using the Saranas EBBMS. Following completion of the procedure subjects will continue to be monitored using the Saranas EBBMS for internal bleeds for up to 8 hours. The EBBMS will then be removed. A flowchart is provided in **Figure 6**. Adverse events and device effects will be recorded from enrollment of subjects and throughout the procedure, until discharge of subjects.

Figure 6. Study Flowchart



3.6 Study Procedures and Assessments

The following procedures and assessments will be performed during the study. For the Schedule of Events see **Table 1**.

3.6.1 Laboratory Assessments

- Blood Chemistry: creatinine,
- Hematology: CBC, PT, PTT, INR

3.6.2 Subject Monitoring and Care

The institutions standard of care monitoring procedures and post-procedural care practices will be followed.

3.6.3 Endovascular Access Procedure

The type of endovascular procedure and the indication for treatment will be recorded. The procedure will be performed according to the institution's standard practices.

3.6.4 Vital Signs

Blood pressure, heart rate, respiration, temperature.

3.6.5 CT Scans

CT scans (with or without contrast) will be optimally (not mandatory) performed prior to the endovascular access procedure to assess for the presence of prior recent bleeding events or vascular complications (i.e. pseudonaeurysm, fistula). Following the procedure, a CT scan (without contrast, unless otherwise indicated) will be performed to confirm or identify any bleeding events. Reference the Imaging Acquisition Protocol in the Study Procedures Manual.

3.6.6 Bleeding, Vascular Complications, and Acute Kidney Injury Assessment

The VARC-2 definitions will be used for bleeding severity and vascular complications, refer to Table 4 and Table 5. For classification of acute kidney injury refer to the AKIN Classification in Table 6.

Table 4. VARC-2 Definitions Bleeding Severity

Life-threatening or disabling bleeding • Fatal bleeding OR • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR • Overt source of bleeding with drop in hemoglobin >5 g/dL or whole blood or packed red blood cells (RBCs) transfusion >4 units)*
Major bleeding • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of two or three units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND • Does not meet criteria of life-threatening or disabling bleeding
Minor bleeding • Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling, or major

**Given that one unit of packed RBC typically will raise the hemoglobin concentration by 1 g/dl, an estimated decrease in hemoglobin will be calculated.*

Table 5. VARC-2 Definitions Vascular Complications

Major Vascular Complications
1. Any aortic dissection, rupture, left ventricular perforation, or new apical aneurysm/pseudoaneurysm
2. Access site or access-site related vascular injury (dissection, perforation, stenosis, hematoma, etc.) leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment
3. Distal embolization requiring vascular surgery, amputation, or irreversible end organ damage
4. Unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia, or neurological impairment
5. Any new ipsilateral lower extremity ischemia
6. Surgery for access site-related nerve injury
7. Permanent access site-related nerve injury

Minor Vascular Complications

1. Access site or access-site related vascular injury (dissection, perforation, stenosis, hematoma, etc.) NOT leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment
2. Distal embolization treated with embolectomy and/or thrombectomy and NOT resulting in amputation or end organ damage
3. Unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication
4. Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft
5. Percutaneous closure device failure
6. Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

Table 6. Acute Kidney Injury (AKIN Classification)

Stage 1

- Increase in serum creatinine to 150–199% (1.5–1.99 x increase compared with baseline) OR increase of >0.3 mg/dl (>26.4 mmol/l)

Stage 2

- Increase in serum creatinine to 200–299% (2.0–2.99 × increase compared with baseline)

Stage 3

- Increase in serum creatinine to >300% (>3 × increase compared with baseline) OR serum creatinine of >4.0 mg/dl (>354 mmol/l) with an acute increase of at least 0.5 mg/dl (44 mmol/l).

The increase in creatinine must occur within 48 h. †Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.

4.0 STUDY CONDUCT

For the Schedule of Events refer to **Table 1**.

4.1 Screening

Within 14 days prior to the procedure, the following baseline/screening assessments will be performed:

- Informed consent
- Assessment of eligibility
- Demographics
- Medical history
- Indication for endovascular procedure
- Physical exam
- Vital signs
- Hematology (refer to Section 3.6.1)
- Blood chemistry (refer to Section 3.6.1)

4.2 Patient Enrollment

After signing Informed Consent, and after study eligibility has been confirmed, patients will be enrolled in the study. A Subject Number will be assigned.

4.3 Endovascular Procedure

4.3.1 Pre-Endovascular Procedures

The following assessments and procedures will be performed prior to the endovascular procedure:

- The endovascular procedure will be planned.
- CT scans (with or without contrast) will be optimally (not mandatory) performed prior to the endovascular access procedure to assess for the presence of prior recent bleeding events or vascular complications (i.e. pseudonaeurysm, fistula). CT scan may be performed up to 90 days prior to the procedure.
- Assessment of baseline signs and symptoms

4.3.2 Endovascular Procedure

The endovascular procedure will be performed in accordance with the institution's standard practices. The appropriate Saranas EBBMS sheath size will be selected, at the Investigator's discretion, and introduced per the Instructions for Use (refer to Appendix B). The data to be collected are as follows:

- Type of endovascular procedure

- Type of vessel cannulated with Saranas EBBMS (e.g. femoral artery, femoral vein)
- Access technique (e.g. ultrasound-guided, micro-puncture, anterior vs. posterior puncture)
- Large bore sheath size
- Type of large bore sheath
- Investigator's actions in response to any bleed detection, e.g. anti-thrombotic reversal, termination of the procedure, additional imaging or interventions.
- Recording of adverse events and/or device complications.

The Saranas EBBMS should be inserted in the femoral vein first. Blood sample (CBC, PT, PTT, INR, and creatinine) should be collected from the Saranas EBBMS after its insertion and prior to its activation. Afterwards, ipsilateral large bore access could be achieved.

During the endovascular procedure, the following assessments should be collected:

- Activated clotting time

4.3.3 Post-Endovascular Procedure

After completion of the endovascular procedure the following assessments and procedures will be performed:

- Saranas EBBMS monitoring for up to 8 hours post-procedure
- A non-contrast CT scan (or contrast CT if clinically indicated or preferred) to identify or confirm any bleeds
- CBC, PT, PTT, INR, creatinine and activated clotting time should be collected immediately before removal of the Saranas EBBMS
- Removal of Saranas EBBMS
- Recording of adverse events and/or device complications
- Recording of the number of units of blood transfused
- Prior to discharge, serum CBC, PT, PTT, INR and creatinine
- Subject will be discharged
- Return of device to sponsor for assessment of impedance response.

5.0 ADVERSE DEVICE EFFECTS

An Adverse Device Effect (ADE) is an adverse event related to the use of a medical device. This includes:

- Any adverse event resulting from insufficiencies or inadequacies in the Instructions for Use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device
- Any event that is a result of a use error or intentional misuse.

Adverse Device Effects will be recorded as Adverse Events (AEs) and/or Device Complications (DCs).

5.1 Recording and Reporting Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence in a subject of a clinical investigation associated with use of an investigational product and that does not necessarily have a causal relationship with this product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to use of the product.

5.1.1 Recording Adverse Events

Adverse events with an onset date following enrollment of the subject until the subject completes the study (is discharged) will be collected. Each adverse event will be followed until the adverse event has resolved or stabilized. Subjects should be encouraged to report adverse events spontaneously or in response to general, non-directed questioning. For each AE volunteered by the subject, the Investigator should obtain all the information required to complete the Adverse Event page of the CRF:

- Standard medical terminology for the AE
- Date and time of onset
- Severity of the event
- Relationship between the adverse event and the investigational product or related procedure
- Description of any subject therapy administered and actions required
- Outcome of the AE
- Whether or not the effect was serious and/or unanticipated

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention must be recorded using medical terminology in the source document and on the adverse experience case report form.

Whenever possible, a diagnosis should be given when signs and symptoms are due to common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").

Each adverse event should be reported separately. For example, "nausea and vomiting" should be split into two separate events.

All AEs must be followed until resolution or until a stable clinical endpoint is reached. All measures required for AE management and the ultimate outcome of the AE must be recorded in the source document and reported to the Sponsor.

5.1.2 Laboratory Abnormalities

An abnormal laboratory result not explained by a recorded clinical diagnosis or condition will be considered an adverse event if it is:

- Grade 3 or 4,
- Clinically significant (requires further diagnostic testing or treatment), or
- Considered to be an Adverse Event by the Investigator.

5.1.3 Grading Severity of Adverse Events

The severity of AEs will be graded as follows:

Mild	Awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and with no sequelae.
Moderate	Interferes with the patient's usual activity and/or requires symptomatic treatment.
Severe	Symptom(s) causing severe discomfort and significant impact of the patient's usual activity and requires treatment.

5.1.4 Assigning Relationship of Adverse Events to Study Product

A relationship must be assigned by the Investigator to each reported adverse event, and will be documented as follows:

Not related	The cause of the AE is known and the event is not related to any aspect of study participation.
Unlikely to be related	There is little or no temporal relationship to the study device and/or a more likely alternative etiology exists.
Possibly related	There is a reasonable possibility that the event may have been caused by study participation. The AE has a **timely relationship** to the study procedure(s); **however, follows no known pattern of response**, and an alternative cause seems more likely or there is significant uncertainty about the cause of the event.
Probably related	It is likely that the event was caused by study participation. The AE has a **timely relationship** to the study procedure(s) and **follows a known pattern of response**; a potential alternative cause, however, may explain the event.

Related	A **related** event has a **strong temporal relationship** and an alternative cause is unlikely.

5.2 Serious Adverse Events

5.2.1 Definition of a Serious Adverse Event

A Serious Adverse Event (SAE) is defined as any event meeting any of the following criteria:

- Is life-threatening (immediate risk of death) or fatal
- Requires, or significantly prolongs, inpatient hospitalization
- Results in persistent or significant disability and/or incapacity
- Is a congenital anomaly or birth defect
- Requires medical or surgical intervention to prevent one of the outcomes listed above

5.2.2 Reporting SAEs

Serious Adverse Events (SAE) will be reported to the Sponsor's Safety Officer within 24 hours of the Investigator becoming aware of the event, and a written report provided within 3 business days to:

Joachim F. Wernicke, Ph.D., M.D.
Tel: (317) 815-0120
Cell: (317) 440-2353

A Serious Adverse Event report will be prepared and will contain as much available information concerning the event as possible so that a written reported may be filed with the FDA.

In accordance with Federal regulations, Investigators will be notified of the occurrence of serious and unexpected adverse events. The Investigator must promptly inform the relevant Institution Review Board in accordance with the IRB's policies.

Documentation of submission of SAEs to the IRB must be forwarded to Proxima and the Sponsor and retained in the Investigator's Study File.

5.3 Unanticipated Adverse Device Effects

Any SAE that has been determined to be device or procedure-related should be further classified as anticipated or unanticipated. An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Investigators must report any (potential) unanticipated adverse device effects to the sponsor and their IRB as soon as possible but no later than within 10 working days after the investigator first learns of the event [21 CFR 812.150]. UADEs should be reported immediately via telephone or email to the Sponsor Safety Officer as well as on the eCRF.

5.4 Device Complications

Investigators are instructed to report all possible device deficiencies, malfunctions, misuse or use error observed during the course of the trial. These incidents will be documented in the case report form provided as follows:

Device deficiency: Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunction, use error, and inadequate labeling. They may or may not affect device performance or lead to an adverse event.

Device malfunction: Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the Instructions for Use (IFU) or protocol. device malfunction occurs when the device is used in compliance with the IFU but does not perform as described in the IFU.

Use error: Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. Use error includes slips, lapses and mistakes. An unexpected physiological response of the patient does not itself constitute a use error.

Device misuse: Any use of the investigational device by an investigator that is contradictory to the application described in the Instructions for Use will be categorized as device misuse. This is a form of Use Error.

5.5 Risk/Benefit Analysis

5.5.1 Potential Risks and Discomforts

Enrollment in the trial involves exposure to some risks. Most risks of trial participation are not materially different than those encountered by an individual undergoing a large bore endovascular procedure outside the context of the trial as introducer sheaths are normally used to access the targeted vessels with the Early Bird. However, the use of the Early Bird device may involve exposure to additional risks as well as other potential risks of an unknown nature.

- Blood loss, bleeding or hematoma
- Embolization (micro or macro) with transient or permanent ischemia
- Infection or scarring
- Vascular trauma (dissection, rupture, perforation, tear etc.)
- There is a risk that the procedure may not detect an internal bleed.
- There is a risk of improper use of the device due to inadequate specifications or training.

5.5.2 Methods to Minimize Risks

- Before releasing the patient, confirmation of internal bleeding status with non-contrast CT scan.
- Adequate IFU to ensure proper technique.

- Only doctors who have been trained in the use of the Early Bird device will participate in the study
- Only doctors with the necessary experience in large bore endovascular procedures will participate in this study

5.5.3 Potential Benefits

- Early detection of internal bleeds during the endovascular procedure
- Less or no need for blood transfusions
- Reduction in, or no drop in post-procedural hemoglobin levels.

6.0 STATISTICAL CONSIDERATIONS

6.1 Patient Sample Size Requirements

This study is intended to describe the accuracy and safety of the Saranas EBBMS. A sample of approximately 100 subjects should provide adequate evaluation of the planned endpoints. If 5%, n = 5, of subjects experience a bleed as detected by either the Saranas EBBMS or computerized tomography then the Kappa score remains above 0.7 when there are two or fewer discordant pairs. The 95% confidence interval with two discordant pairs and Kappa of 0.74 ranges from 0.39 to 1.0.

6.2 Primary Efficacy Endpoint

The primary endpoint is the level of agreement in bleeding detection between the Saranas EBBMS and post-procedural computerized tomography.

6.3 Secondary Endpoints

The following secondary endpoints will be assessed:

- Level of agreement in bleeding detection between the Saranas EBBMS and clinical assessment or post-procedural computerized tomography
- Device sensitivity in bleeding detection of the Saranas EBBMS as compared to post-procedural computerized tomography
- Device specificity in bleeding detection of the Saranas EBBMS as compared to post-procedural computerized tomography
- Device sensitivity in bleeding detection between Saranas EBBMS and clinical assessment or post-procedural computerized tomography
- Device specificity in bleeding detection between Saranas EBBMS and clinical assessment or post-procedural computerized tomography
- Relationship between level (severity) of bleed detected by the Saranas EBBMS and the severity of bleeding as assessed by computerized tomography
- Relationship between level (severity) of bleed detected by the Saranas EBBMS and the severity of bleeding as assessed by the absolute drop in hemoglobin
- Relationship between level (severity) of bleed detected by the Saranas EBBMS and the number of transfusions
- Relationship between level (severity) of bleed detected by the Saranas EBBMS and the severity of bleeding as assessed by VARC-2 criteria.
- Relationship between level (severity) of bleed detected by the Saranas EBBMS and the occurrence of post-procedural acute kidney injury

6.4 Safety Endpoints

From enrollment until end of study, all:

- Device and procedure-related adverse events
- Serious adverse events
- Serious adverse device effects

6.5 Study Populations

Intent to Treat Population: The Intent to Treat (ITT) population is defined as all subjects who were enrolled in the study.

Per Protocol Population: The Per Protocol (PP) population is defined as all subjects who had a post-procedure computerized tomography.

Safety Population: The Safety Population is defined as all subjects who are enrolled, who receive study intervention, and who have some post-baseline assessment of safety data.

6.6 Statistical Analytical Plan

6.6.1 Demographics and Subject Characteristics

For all subjects included in this study, baseline demographic and medical history data will be summarized for each treatment group. Summaries for quantitative variables include the sample size, mean, median, standard deviation, minimum, and maximum. Summaries for categorical variables include the number and percent of patients for each outcome. No statistical testing will be performed to compare these factors. These summaries will be conducted in the all three populations, ITT, PP and Safety.

6.6.2 Assessment of Endpoints

Primary Endpoint

The primary endpoint is the level of agreement in bleeding detection between the Saranas EBBMS and post-procedural computerized tomography. Each case will be defined dichotomously as bleed or no bleed by both techniques. This analysis will be conducted in the PP population of subjects who has a post-procedure computerized tomography.

Level of agreement will be assessed using Cohen Kappa statistic. A 95% confidence interval will be applied. A good Kappa score is considered to be at 0.6 or greater. for dichotomous endpoints. Each case will be defined as a bleed or no bleeding.

Table 7. Interpretation of Kappa Values

kappa	Level of Agreement
0	Equal to chance
$0<k\leq0.20$	Poor
$0.21<k\leq0.40$	Fair
$0.41<k\leq0.60$	Moderate
$0.61<k\leq0.80$	Good
$0.81<k\leq0.99$	Excellent
1	Perfect

Secondary Endpoints

Device specificity and sensitivity will be defined as follows:

Sensitivity will be assessed as:

$$\text{Sensitivity} = \frac{\text{Number of subjects with Confirmed Bleeds}}{\text{Number of subjects with Confirmed Bleeds + number of False Negatives}}$$

A *Confirmed Bleed* is a bleed detected by the Saranas EBBMS that is also confirmed by CT scan and/or clinical assessment.

A *False Negative* is a bleed that is not detected by the Saranas EBBMS that *is* detected by CT scan and/or clinical assessment.

Device specificity, assessed as:

$$\text{Specificity} = \frac{\text{Number of subjects Confirmed with No Bleeds}}{\text{Number of subjects Confirmed with No Bleeds + number of False Positives}}$$

Confirmed with no bleeds is no bleed detected by the Saranas EBBMS that is confirmed by CT scan and/or clinical assessment.

A *False Positive* is a bleed detected by the Saranas EBBMS that is *not* confirmed by CT scan and/or clinical assessment.

The following secondary endpoints will be investigated:

- Level of agreement in bleeding detection between the Saranas EBBMS and clinical assessment or post-procedural computerized tomography will be calculated in a manner similar to specified for the primary endpoint. This analysis will be conducted in both the PP and ITT population with the clinical determination of a bleed overruling any computerized tomography or missing assessment.
- Device sensitivity in bleeding detection of the Saranas EBBMS as compared to post-procedural computerized tomography will be calculated in the PP population.
- Device specificity in bleeding detection of the Saranas EBBMS as compared to post-procedural computerized tomography will be calculated in the PP population.
- Device sensitivity in bleeding detection between Saranas EBBMS and clinical assessment or post-procedural computerized tomography will be calculated. This analysis will be conducted in both the PP and ITT population with the clinical determination of bleed overruling any computerized tomography or missing assessment.
- Device specificity in bleeding detection between Saranas EBBMS and clinical assessment or post-procedural computerized tomography will be calculated. This analysis will be conducted in both the PP and ITT population with the clinical determination of bleed overruling any computerized tomography or missing assessment.
- Relationship between level (severity) of bleed detected by the Saranas EBBMS and the severity of bleeding as assessed by computerized tomography will be investigated. Summary statistics and interclass correlations will be calculated to assess the relationship between the two variables.
- Relationship between level (severity) of bleed detected by the Saranas EBBMS and the severity of bleeding as assessed by the absolute drop in hemoglobin from baseline will be investigated. Summary statistics and interclass correlations will be calculated to assess the relationship between the two variables.
- Relationship between level (severity) of bleed detected by the Saranas EBBMS and the number of transfusions will be investigated. Tabulations, summary statistics and interclass correlations will be used to describe the relationship between these two variables.
- Relationship between level (severity) of bleed detected by the Saranas EBBMS and the severity of bleeding as assessed by VARC-2 criteria will be investigated. Tabulations, summary statistics and interclass correlations will be used to describe the relationship between these two variables.
- Relationship between level (severity) of bleed detected by the Saranas EBBMS and the occurrence of post-procedural acute kidney injury will be investigated. Summary statistics and interclass correlations will be calculated to assess the relationship between the two variables.

6.6.3 Assessment of Safety

Safety will be assessed from device and procedure-related adverse events, serious adverse events and serious adverse device effects.

Safety and tolerability will be assessed by evaluating reported AEs as well as any changes in values from baseline of clinical laboratory assessments.

The incidence of treatment-emergent AEs will be reported overall and by severity and relatedness to study intervention. AEs causing study discontinuation and serious adverse events will be listed and tabulated.

6.6.4 General Statistical Issues

Descriptive statistics to be reported for each analyzed variable will include the number of observations, mean, median, standard deviation and range for quantitative variables, frequency and relative percent for ordinal and categorical variables.

Summary statistics will be displayed in tabular and/or graphical format. Missing data will not be interpolated, other than when a clinical assessment can replace a missing computerized tomography assessment. Any hypothesis tests will be performed using a two-sided significance level of 0.05. All computations will be performed using SAS®, version 9.1 or higher.

7.0 REGULATORY AND ADMINISTRATIVE REQUIREMENTS

7.1 Accountability of Investigational Product

The Investigator is required to maintain adequate records of the disposition of the investigational product, including dates, quantity, and use by subjects throughout the study. Records will be kept on product accountability and inventory forms. If the investigation is terminated, suspended, discontinued, or completed, or upon instruction from the Sponsor. the Investigator shall return the unused supplies to the Sponsor, in the original containers, to:

C.G. Laboratories, Inc.
1410 Southtown Drive
Granbury, TX 76048

The Investigator will not supply investigational study product to other investigators, nor allow use of investigational study product other than to patients registered on, and as directed by, this protocol. The Investigator will dispense investigational product only from the designated investigational site.

Accountability of study product will be verified by the Sponsor's Study Monitor during on-site monitoring visits.

7.2 IRB Requirements

United States Federal regulations require that all investigational product studies be conducted under the auspices of an Institutional Review Board (IRB), as defined in the Code of Federal Regulations, Title 21, Part 56. This committee, the makeup of which must conform to the Federal, State and local guidelines regarding such, will approve all aspects of the Study, including said Protocol and Informed Consents to be used, prior to initiation. The formal written approval notice must be signed by the chairman or authorized designee and must identify the specific protocol. In cases where an IRB member has a conflicting interest, abstention of that individual from voting should be documented. The investigator will provide the Sponsor with a copy of the communication from the Committee to Investigator indicating approval of the protocol and consent form. All changes to the protocol and consent form must be reviewed and approved prior to implementation, except where necessary to eliminate apparent immediate hazards to human subjects.

The Investigator must also report to the IRB, at least annually, on the progress of the investigation. Continuing IRB review should be documented by a letter from the IRB. Notification to the IRB by the Investigator within three months after completion, termination, or discontinuation of the study at the specific site must be documented.

7.3 Protocol Amendments

Amendments will originate from the Sponsor and will be provided to the Investigator for submission to his/her IRB for their review and approval prior to implementation. It should be noted that when an amendment to a protocol substantially alters the study design or increases potential risk to the study patient, the informed consent should be revised and if applicable, patient's consent to continue participation should again be obtained.

No deviations from the protocol should be made except in emergency situations where

alternative treatment is necessary for the protection, proper care and wellbeing of patients. In situations requiring a departure from the protocol, the Investigator or other physician in attendance will contact the Sponsor's Clinical Representative by fax or telephone. If possible, this contact will be made before implementing any departure from the protocol. In all cases, contact with the Sponsor's Clinical Representative must be made as soon as possible in order to discuss the situation and agree on an appropriate course of action. The case report form and source document will describe any departure from the protocol and the circumstances requiring it.

7.4 Informed Consent

The Investigator will be responsible for obtaining from every patient prior to his/her participation in the Study an Informed Consent signed by the patient or legally authorized representative, in accordance with the code of Federal Regulations, Title 21, Part 50.20. The consent form that is used must be the current version and must be approved by both the reviewing IRB and by the Sponsor. Informed consent will be obtained from the patient after a full explanation of the purpose of the study, risks and discomforts involved, potential benefits, etc. have been provided by the Investigator both verbally and in writing. The original signed copy of the informed consent must be maintained in the institution's records, and is subject to inspection by a Sponsor representative.

7.5 Confidentiality

The sponsor is concerned for the individual patient's privacy; therefore, all collected patient data will be treated confidentially, identified only by a patient identification number and patient initials.

In compliance with federal guidelines regarding the monitoring of clinical studies and in fulfillment of the Investigator's obligation to the Sponsor, it is required that he/she permit the Sponsor Study Monitor or Food and Drug Administration (FDA) representative to review that portion of the patient's medical record that is directly related to the study. This shall include all study relevant documentation (including medical histories to verify eligibility, laboratory tests results to verify transcription accuracy, treatment and diagnostic reports, admission/discharge summaries for hospital admissions occurring while the patient is on study, and autopsy reports for deaths occurring during or in temporal proximity to the study).

As part of the required content of informed consent, the patient must be informed that his/her records will be reviewed by the Sponsor, the Study Monitor or a representative of the Food and Drug Administration. Should access to the medical record require a separate waiver or authorization, it is the Investigator's responsibility to obtain such permission from the patient in writing before the patient is entered into the study.

All information provided to the Investigator by the Sponsor, including nonclinical data, protocols, CRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting this study, and no disclosure shall be made except in accordance with any right of publication granted to the Investigator.

7.6 Required Regulatory Documents

It is the responsibility of the Investigator and study staff to maintain a comprehensive and centralized filing system of all study-related documentation, which is suitable for inspection at any time by the Study Monitor and the FDA. Elements should include:

- Patient files containing the completed Case Report Forms, supporting source documentation and the Informed Consent.
- Pharmacy or Investigator files, containing the Investigational Product Accountability Records or dispensation logs and all study product related correspondence.
- Study files, containing the following required documentation:
  - Protocol with all amendments
  - Copies of all pre-study documentation and all correspondence to and from the IRB and the Sponsor or Sponsor representatives
  - An up-to-date curriculum vitae for the Principal Investigator.
  - Signed and dated Investigator Agreement.
  - Assurance that the reviewing IRB complies with the requirements set forth in Title 21 Part 56 of the Code of U.S. Federal Regulations. The required documentation will consist of the name and address of the IRB/EC and a list of its members, including their titles, occupations, and any institutional affiliations, or a Department of Health and Human Services Assurance number.
  - A copy of the formal written notification to the Investigator regarding approval of the protocol by the IRB.
  - A copy of the IRB approved informed consent form and other adjunctive materials (e.g., advertising) to be used in the study, including written documentation of IRB approval of these items.
  - A copy of the reference ranges for clinical laboratory evaluations and a copy of the certification of the laboratory facility.
- In addition to the documents required prior to the study, other documentation may be required during the course of the study.

7.7 Record Retention

The FDA requires that an Investigator retain study records for a period of two (2) years following the date that a marketing application is approved for the indication in which the study product is being investigated; or if no application or license is to be filed or if the application or license is not approved for such an indication, until two (2) years after the FDA is notified that the indication is discontinued.

Study records include: all case report forms and all source documents (e.g., informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnoses and dates of therapy prior to and during this study, device dispensing/disposition records) that support data entered on case report forms.

If the Investigator for any reason desires to dispose of the records, they may be transferred to another institution, another investigator, or to the Sponsor upon written agreement between the Investigator and the Sponsor.

7.8 On-Site Audits

The FDA, in the person of a trained and properly authorized employee of the department, may request access to all study records, including source documents, for inspection and copying, in keeping with FDA regulations. The Investigator should immediately notify the Sponsor of an upcoming inspection. An auditing inspection may also be conducted by a representative of the Sponsor's Clinical Quality Assurance Department.

7.9 Case Report Form Completion

Case report forms are provided for each patient. All forms must be legibly filled out in black ink or typed. Data will be entered into the CRF as information becomes available on a visit-by-visit or course-by-course basis. The Study Completion Information page of the case report form must be signed and dated by the Principal Investigator.

All case report form corrections are to be made by an Investigator or other study site personnel. The Principal Investigator or sub-investigator must authorize changes to the recorded safety and efficacy data.

The Principal Investigator or a Sub-investigator will sign and date the indicated places of the Case Report Form. This signature will indicate that thorough inspection of the data therein has been made and will thereby certify the contents of the form.

7.10 Study Completion/Termination

The Investigator will complete the study and submit the case report forms in satisfactory compliance with the protocol within an agreed upon time frame for each center after receipt of clinical supplies. Continuation of this study beyond this time must be agreed upon by both the Investigator and the Sponsor and may be implemented without amendment to the protocol. It is agreed that for reasonable cause, either the Investigator or the Sponsor may terminate this study before the above time, provided notice is provided at a reasonable time in advance of the intended termination.

7.11 Monitoring Procedures

Clinical research staff (CRAs) designated by the Sponsor will visit the study center periodically to monitor adherence to the protocol and to applicable FDA regulations, and the maintenance of adequate and accurate clinical records. Monitoring functions will be performed in compliance with recognized Good Clinical Practices. The Investigator agrees to allow these CRAs, and other authorized Sponsor personnel, access to the clinical supplies, the investigational product dispensing and storage area, patient medical records, laboratory data, and other source documentation of the study patients.

Case Report Forms will be reviewed in detail by the Study Monitor who will make a decision as to their acceptability. If errors or omissions are found in the course of a data audit, or if clarification of data is required, the Case Report Form(s) in question will be corrected by the Investigator or designee. Data Clarification or Query Forms may be generated for omissions or clarifications, to be completed and returned to the Study Monitor.

The dates of monitoring visits will be recorded by the Study Monitor in a sign-in log to be kept at the site. The Sponsor expects that, during monitoring visits, the study coordinator and

Investigator will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents. The Investigator agrees to assist Sponsor personnel in their duties, if requested.

7.12 Use of Information and Publication Policy

The information provided in support of or generated as a result of this study is confidential. Any use or reproduction thereof, including but not limited to publications or presentations by the Investigator or his associates, must be submitted to the Sponsor for review and approval prior to publication or presentation in any form. All publications must acknowledge the sponsorship.

All information not previously published concerning information such as patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by the Sponsor to the Investigator is considered confidential and shall remain the sole property of the Sponsor. The Investigator agrees to use this information only to accomplish this study and will not use it for other purposes without the Sponsor's written consent.

The Investigator understands that the information developed in the clinical study will be used by the Sponsor in connection with the continued development of the study product, and may thus be disclosed as required to other clinical Investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.

7.13 Ethical and Legal Considerations

This study will be conducted in compliance with all applicable laws and regulations of the state and institution where the patient is treated, in accordance with the Declaration of Helsinki, and according to the guidelines in this protocol, including attached appendices.

The investigator is responsible for the retention of the patient log and patient records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and not be publicly available.

8.0 REFERENCES

1. Nguyen CT, Lee E, Luo H, Siegel RJ. Echocardiographic guidance for diagnostic and therapeutic percutaneous procedures. Cardiovasc Diagn Ther. 2011;1(1):11-36.
2. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. Circulation. 2011;123(4):e18-e209.
3. Seldinger SI**.** Catheter replacement of the needle in percutaneous arteriography; a new technique. Acta radiol. 1953;39(5):368-76.
4. Babu SC, Piccorelli GO, Shah PM, Stein JH, Clauss RH**.** Incidence and results of arterial complications among 16,350 patients undergoing cardiac catheterization. J Vasc Surg. 1989;10(2):113-6.
5. Chandrasekar B, Doucet S, Bilodeau L, Crepeau J, deGuise P, Gregoire J, et al. Complications of cardiac catheterization in the current era: a single-center experience. Catheter Cardiovasc Interv. 2001;52(3):289-95.
6. Vavalle JP, Rao SV**.** Impact of bleeding complications on outcomes after percutaneous coronary intervention. Interventional Cardiology. 2009;1(1):11.
7. Kinnaird TD, Stabile E, Mintz GS, Lee CW, Canos DA, Gevorkian N, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. Am J Cardiol. 2003;92(8):930-5.
8. Yatskar L, Selzer F, Feit F, Cohen HA, Jacobs AK, Williams DO, et al. Access site hematoma requiring blood transfusion predicts mortality in patients undergoing percutaneous coronary intervention: data from the National Heart, Lung, and Blood Institute Dynamic Registry. Catheter Cardiovasc Interv. 2007;69(7):961-6.
9. Moscucci M, Fox KA, Cannon CP, Klein W, Lopez-Sendon J, Montalescot G, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). Eur Heart J. 2003;24(20):1815-23.
10. Crudu V, Blankenship J, Berger P, Scott T, Skelding K**.** Complications related to access site after percutaneous coronary interventions: are the adverse events underreported? Catheter Cardiovasc Interv. 2011;77(5):643-7.
11. Sherev DA, Shaw RE, Brent BN**.** Angiographic predictors of femoral access site complications: implication for planned percutaneous coronary intervention. Catheter Cardiovasc Interv. 2005;65(2):196-202.
12. Kent KC, Moscucci M, Mansour KA, DiMattia S, Gallagher S, Kuntz R, et al. Retroperitoneal hematoma after cardiac catheterization: prevalence, risk factors, and optimal management. J Vasc Surg. 1994;20(6):905-10; discussion 10-3.
13. Fruhwirth J, Pascher O, Hauser H, Amann W**.** [Local vascular complications after iatrogenic femoral artery puncture]. Wien Klin Wochenschr. 1996;108(7):196-200.
14. Berry C, Kelly J, Cobbe SM, Eteiba H**.** Comparison of femoral bleeding complications after coronary angiography versus percutaneous coronary intervention. Am J Cardiol. 2004;94(3):361-3.

15. Khoury M, Batra S, Berg R, Rama K, Kozul V**.** Influence of arterial access sites and interventional procedures on vascular complications after cardiac catheterizations. Am J Surg. 1992;164(3):205-9.

APPENDIX A: INVESTIGATOR AGREEMENT

Provision of my signature below indicates my desire to participate in the clinical investigation of Saranas, Inc's Early Bird Bleed Monitoring System and my agreement to all terms of this Investigator Agreement.

I have thoroughly familiarized myself with the Investigation Plan (protocol) for the clinical study of the Saranas Early Bird Bleed Monitoring System and I believe that I am an individual who, because of my training and experience, is qualified to investigate the performance of the Saranas Early Bird Bleed Monitoring System under the purview of an appropriate Institutional Review Board (IRB) or Ethics Committee.

I specifically and further agree that:

1. I will conduct the clinical investigation in accordance with this Investigator Agreement, the Investigation Plan, the FDA IDE regulations, other pertinent FDA regulations, and any conditions imposed by my IRB, Ethics Committee or federal/state/local regulatory agencies.
2. I will submit a copy of the written approval by my IRB/Ethics Committee of the Investigational Plan to the Sponsor prior to enrollment of the first patient.
3. Prior to any study related procedure, I will obtain a signed Informed Consent from every patient, or his/her legal representative, who participates in this clinical investigation.
4. I agree to complete all training required by the Sponsor in the use of Saranas Early Bird Bleed Monitoring System prior to treatment of the first patient. I will review all investigational product and study-related documents sent to me by the Sponsor in a thorough and timely fashion and will provide the Sponsor with pertinent feedback when requested.
5. All use of Saranas Early Bird Bleed Monitoring System will be under my direct supervision and according to the approved Investigational Plan. I will not allow access to Saranas Early Bird Bleed Monitoring System to anyone other than those employees of my institution who, under my direct supervision, are participating in this study.
6. Only patients satisfying the study inclusion/exclusion criteria and willing to provide informed consent will be enrolled into this clinical trial.
7. All information received from the Sponsor about Saranas Early Bird Bleed Monitoring System, and all knowledge obtained under or concerning this study including the study design, protocol, data, results, and any related written or orally-transmitted information, is considered the proprietary property of the Sponsor, and I will retain it in confidence and not release it to anyone without written consent from the Sponsor.
8. I will ensure that investigational data are collected and recorded in a complete and accurate manner. I will sign all case report forms as testimony to my review of investigational data. I understand that it is necessary that investigational data be submitted to the Sponsor within seven days of collection so as to ensure a timely review and assimilation of results.
9. I agree to personally meet with, and implement any corrective actions identified by, the Sponsor's study monitors during periodic audits.
10. Provide all required data and reports and agree to source document verification of study data with patient's medical records by Sponsor (or designee) and any regulatory authorities.

11. I will submit interim and final reports to my IRB/Ethics Committee, the FDA and my federal, state, and local regulatory agencies as required by the conditions of approval from the respective agencies.
12. Allow Sponsor personnel or its designees, as well as regulatory representatives, to inspect and copy any documents pertaining to this clinical investigation according to national data protection laws
13. I will obtain written permission in advance from the Sponsor to publish or present any aspect of the Investigational Plan and study, including, but not limited to, animal or human study design, data, and results.
14. I agree to fully comply with all of the responsibilities of Investigators outlined in the Code of Federal Regulations.

I have never participated in any research project that has been terminated by an administrative body, financial sponsor, or regulatory agency for reasons of protocol noncompliance, misrepresentation of data, or any other reason.

Printed Name of Investigator:_____

Signature of Investigator: _____ Date:_____

APPENDIX B. INSTRUCTIONS FOR USE

INSTRUCTIONS FOR USE (IFU)

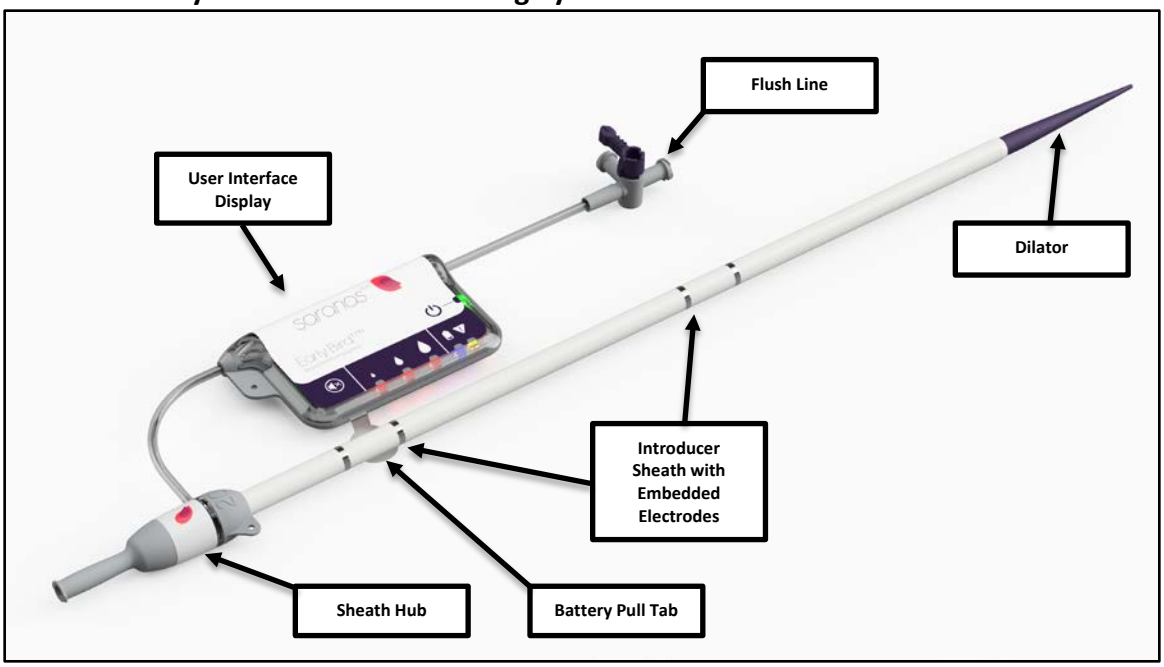
Saranas™ Early Bird™ Bleed Monitoring System

CAUTION: “Investigational Device. Limited by Federal (or United States) law to investigational use.” per 21 CFR 812.5. This product has not been approved for marketing in the United States, and is not available for commercial sale in the United States.

Carefully read all instructions prior to use. Observe all warnings and precautions noted throughout these instructions. Failure to do so may result in complications.

1 DESCRIPTION

FIGURE 1: Early Bird™ Bleed Monitoring System



The Early Bird consists of the following: introducer sheath, user interface display (UID), for the early detection and monitoring of potential internal bleeding complications, and a dilator as shown in **Figure 1**. The introducer sheath contains four embedded electrodes. The distal end of the sheath has a tapered leading edge which transitions smoothly to the tapered dilator, forming an atraumatic device. The dilator is radiopaque to aid in visibility under fluoroscopy during insertion.

TABLE 1: Sizing Table

Size (French)	Minimum Sheath Internal Diameter, inches (mm)	Working Length (cm)	Working Length w/ Dilator (cm)
6	0.085 (2.16)	20	23
8	0.110 (2.79)	20	23
14	0.192 (4.88)	20	23

2 PACKAGE CONTENTS

- Early Bird Bleed Monitoring System
- Dilator
- Directions for Accessing IFU

3 INTENDED USE

The Early Bird is intended:

- to be inserted in the vasculature to provide a conduit for the insertion of endovascular devices while minimizing blood loss associated with such insertions.
- to provide physicians with an early indication of extravascular fluid accumulation, which may be due to a potential internal bleeding complication.
- to detect and monitor changes in bioimpedance due to extravascular fluid accumulation, and to provide physicians with indications that a potential internal bleeding complication is progressing.

The Early Bird is intended to provide physicians and other healthcare providers with additional information to aid in their clinical assessment of the patient during and after endovascular access procedures. As such, it is not intended to diagnose or replace clinical judgment of healthcare professionals.

Physicians are encouraged to follow accepted clinical practices when treating a potential internal bleeding complication, including cessation or reversal of anti-coagulants and application of pressure near the site of vascular access.

4 INDICATIONS

The Early Bird is indicated for use in endovascular procedures such as:

- Endovascular Aneurysm Repair (EVAR, including abdominal aortic aneurysms)
- Transcatheter Aortic Valve Implantation (TAVI) or Replacement (TAVR)
- Hemodynamic support devices such as intra-aortic balloon pump (IABP), percutaneous ventricular assist device (PVAD) and enhanced extracorporeal

membrane oxygenation (ECMO)

- Percutaneous Coronary Intervention (PCI)
- Transcatheter structural heart procedures such as balloon valvuloplasty, mitral valve repair, or mitral valve replacement
- Other similar procedures which utilize introducer sheaths to gain vascular access.

The device provides physicians with an early indication of a potential internal bleeding complication by initial detection and monitoring of extravascular fluid accumulation.

5 CONTRAINDICATIONS

- Only one Early Bird may be used during a procedure. If more than one introducer sheath is required simultaneously to perform a procedure, use a standard introducer sheath in the secondary position.

6 WARNINGS

- Carefully read all instructions prior to use. Observe all warnings and precautions noted throughout these instructions. Failure to do so may result in complications.
- Only physicians who have received appropriate training and are familiar with the principles, clinical applications, side effects and hazards commonly associated with vascular interventional procedures should use this device.

- This device is not MRI compatible.
- The Early Bird may not detect an Internal Bleeding Complication if internal bleeding has already occurred prior to insertion of the introducer sheath or prior to initial bioimpedance measurement.
- The Early Bird should not be exposed to organic solvents.
- Do not alter this device, including cutting to alter the length. Alterations may impair device function.
- Do not attempt to place a guidewire with a maximum diameter greater than 0.035” (0.89 mm) through the dilator.
- Do not attempt to insert a catheter or interventional device having a diameter larger than the introducer sheath size (Table 1). Device damage or breakage may result.
- Do not attempt to insert multiple catheters or interventional devices when the combined diameter is larger than the introducer sheath size (Table 1). Device damage or breakage may result.
- Do not attempt sheath advancement or withdrawal without guidewire and dilator in place. Major bleeding, vessel damage or serious injury to the patient, including death, may result.

- Adequate vessel access is required to introduce the sheath into the vasculature. Careful evaluation of vessel size, anatomy, tortuosity, and disease state (including calcification, plaque, and thrombus) is required to ensure successful sheath introduction and subsequent withdrawal. If the vessel is not adequate for access, major bleeding, vessel damage, or serious injury to the patient, including death, may result.
- Do not advance the sheath if the dilator is not snapped in the hemostasis valve housing. When the dilator is not snapped into the valve housing, the tip of the introducer sheath may not be fully supported by the cylindrical section of the dilator. Therefore, advancement of the unsupported tip of the introducer sheath may result in major bleeding, vessel damage, or serious injury to the patient, including death.
- Do not attempt to advance or withdraw guidewire, catheter, or other device through the introducer sheath or dilator if resistance is felt. Use fluoroscopy to determine the cause. Continued advancement or retraction against resistance may result in major bleeding, vessel damage, serious injury to the patient, or damage to/breakage of the guidewire, catheter, or other device.
- Advance dilator and sheath assembly together with a twisting motion to minimize vessel trauma.
- Advance and remove sheath only under fluoroscopic guidance.
- Use an appropriate wire guide to introduce additional guidewires through the hemostasis valve alongside the previously placed guidewire, catheter, or other interventional device. Advancement of guidewires without the appropriate wire guide through the valve may result in damage to the guidewire or the valve. Damage to the valve could result in major blood loss.

7 PRECAUTIONS

- Do not attempt to advance sharp objects/instruments through the hemostasis valve. Sharp objects/instruments could cause damage to the valve and could result in major blood loss.
- Do not puncture the valve. Puncturing the valve could result in major blood loss.
- Examine packaging and device before use. Do not use if either the packaging or device is damaged, or if the sterile barrier has been compromised.
- Do not use after the use by (expiration) date printed on the label.
- Do not re-sterilize; for single use only.
- The Early Bird is designed for single use only; do not re-use this device. Saranas does not have data regarding re-use of this device. Re-use may cause device failures or procedural complications, including device damage, compromised device biocompatibility, and device contamination. Re-use may result in blood loss, infection, serious injury, or patient death.
- To prevent or reduce the risk of clot formation, consider using systemic

anticoagulation and keeping the introducer sheath filled with an appropriate heparinized flushing solution when it is in the vessel.

- Verify sheath, device, catheter, and accessory components size compatibility prior to use.
- Individual patient anatomy and physician techniques may require procedural variations.

8 POTENTIAL ADVERSE EVENTS

Adverse events that may occur and require intervention include, but not limited to:

- Blood loss, bleeding, hematoma
- Embolization (micro or macro) with transient or permanent ischemia
- Infection
- Vascular trauma (i.e. dissection, rupture, perforation, tear, etc.)
- Death

9 HOW SUPPLIED

- The Early Bird is supplied sterile and non-pyrogenic.

10 STORAGE AND HANDLING

- Store in a cool, dry place.

11 REQUIRED ACCESSORIES

- 0.035” (0.89 mm) Guidewire
- Heparinized Saline

12 DIRECTIONS FOR USE

12.1 Sheath Preparation

12.1.1 Verify the proper size introducer sheath is selected for the device to be introduced.

12.1.2 Verify the vessel is of adequate diameter and tortuosity to accommodate the introducer sheath.

12.1.3 Remove the introducer sheath and dilator from its packaging and examine contents for possible damage or defects.

Caution: Do not use if damaged or defective.

Caution: <u>Do not pull the UID battery pull tab</u> prior to insertion of the sheath into the vasculature and prior to suturing the sheath in place. Once the battery pull tab is pulled, the device automatically powers on and allows

five (5) minutes for the bleed monitor to detect a bioimpedance signal before the device locks into an error state, after which, the device will not function as intended. Refer to Section 13 if the device is in an error state.

12.1.4 Prior to insertion, wipe down the introducer sheath and dilator with heparinized saline. Do not wipe the surface with dry gauze.

12.1.5 Flush the sheath through the stopcock with heparinized saline. Close the stopcock.

12.1.6 Flush the dilator through the proximal hub with heparinized saline.

12.1.7 Carefully insert the dilator tip through the hemostasis valve and into the sheath until the dilator hub is adjacent to the hemostasis valve. Gently snap the dilator hub into the hemostasis valve housing to ensure the tapered portion of the dilator is beyond the distal end of the introducer sheath making a smooth, atraumatic transition.

12.2 **Sheath Introduction and Use**

12.2.1 Using standard Seldinger technique, access the target vessel with the appropriate needle.

12.2.2 Insert a 0.035" (0.89 mm) guidewire through the needle and into the vessel, then remove the needle ensuring the guidewire remains positioned within the vessel.

12.2.3 Advance the distal end of the dilator over the guidewire.

12.2.4 Advance the assembly (sheath/dilator) as a unit over the guidewire under fluoroscopic guidance; do not allow the dilator to back out of the sheath while advancing. Use a slight twisting motion to advance the assembly through the tissue and into the target vessel. Stop advancement of the assembly if resistance is felt. Investigate the cause of resistance before proceeding. Carefully advance the assembly until it is fully inserted.

Caution: Do not attempt advancement of the sheath without the dilator and guidewire in place. Major bleeding, vessel damage, or serious injury to the patient, including death, may result.

12.2.5 Hold the sheath steady and maintain guidewire position while withdrawing the dilator from the sheath until it is completely removed from the guidewire.

12.2.6 Aspirate and flush the introducer side-arm.

12.2.7 Carefully suture the sheath in place to minimize device movement during use.

12.2.8 Pull the battery pull tab to activate the Early Bird.

Do not press the power button at this time. The power button is

only used to turn off the device within the first five (5) minutes.

12.2.9 Carefully support all guidewires, catheters, and other devices while advancing through the valve and sheath.

12.2.10 Advance the selected interventional device over a guidewire through the valve and sheath. Follow manufacturer's recommendations for use of the selected interventional device.

Caution: Do not advance or retract interventional devices into or out of the sheath if resistance is felt. Determine the cause of resistance before proceeding.

Caution: Do not attempt to advance sharp objects/instruments through the valve. Damage to the valve may result in major blood loss.

Caution: Advancement of guidewires without an appropriate wire guide through the valve may result in damage to the guidewire or the valve. Damage to the valve could lead to major blood loss.

12.3 **Sheath Removal**

12.3.1 Reintroduce a 0.035" guidewire, if not already placed.

12.3.2 Insert the dilator over the guidewire and into the sheath and snap dilator into the sheath hub.

12.3.3 Gently rotate the sheath to ensure the sheath is free from the vasculature.

12.3.4 While maintaining the guidewire position, pull the sheath proximally until the sheath is fully removed. The yellow Device Error indicator will illuminate, and the audible indicator will momentarily beep. During removal of the sheath, precautions should be taken to prevent excessive blood loss, vessel damage, or other serious injury.

12.3.5 Follow standard clinical procedure to close the site after device removal.

12.3.6 Follow standard hospital procedure for device disposal.

13. FUNCTIONALITY

The Early Bird provides early detection of potential internal bleeding complications and monitors for internal bleeding progression based on baseline bioimpedance measurements and bioimpedance changes throughout the course of a procedure. The device correlates the bioimpedance signal to changes in extravascular fluid accumulation and displays bleeding status to the physician through a series of Light-Emitting Diodes (LED's) located on the UID (as shown in **Figure 2**).

FIGURE 2: Early Bird™ UID

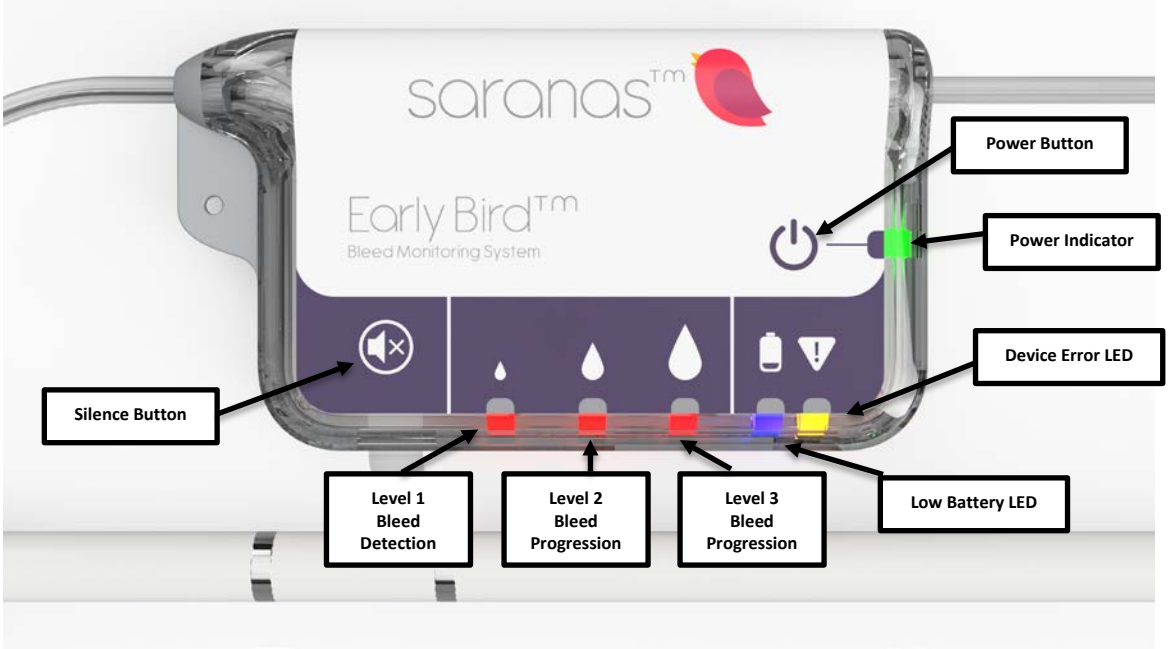


TABLE 2: Indicator Descriptions

LED/Indicator	Description
Bleed Monitoring (Red) 	The red Bleed Monitoring indicators are a series of three (3) LED's that sequentially illuminate as bioimpedance continues to change over the course of a procedure, indicating a possible internal bleeding complication. • Level 1 indicator (1st LED) is triggered by the early onset of a bleed. An audible alert is momentarily activated once this level is triggered. • Level 2 indicator (2nd LED) is triggered as the bleed progresses when a bioimpedance threshold is reached. An audible alert, longer in duration than the 1st LED, is momentarily activated once this level is triggered. • Level 3 indicator (3rd LED) is triggered as the bleed continues to progress further when a higher bioimpedance threshold is reached. An audible alert is activated once this level is triggered and requires the attending physician to silence the device by pressing the silence button.
Low Battery (Blue)	The blue Low Battery indicator will blink when the battery is near end of life. The audible indicator will momentarily beep.

	If the system shuts down due to a low battery, the device has reserved enough power so that the system can be powered on to observe the last state of bleed monitoring indicators.
Device Error (Yellow) 	The yellow Device Error indicator will illuminate when an internal system error has been detected. The audible indicator will momentarily beep. If the yellow Device Error is illuminated, press and hold the Power button to turn off the device and turn the device back on for one additional attempted use of bleed detection and monitoring. If the yellow Device Error illuminates again, the device cannot be used. Once the procedure is completed, report the event to Saranas.
Power (Green) 	The green Power indicator will blink after the device is first turned on and until it detects a bioimpedance signal which is in an acceptable range. Then, the indicator will stop blinking and remain illuminated throughout the procedure.
Button	**Function**
Silence 	This button is used to silence the audible indicator.
Power 	After the battery pull tab is pulled, the system will run through a series of self-tests which will illuminate all indicators. The audible indicator will momentarily beep. If required, press and hold the button to turn off the device. Note that the device can be turned off only within the first five (5) minutes after powering on the device.

14. TECHNICAL DESCRIPTION

Battery

Battery Type: Alkaline 1.5V AAA

Battery Life: Up to 12 hours

The Early Bird battery is non-serviceable.

Electrical Safety

ME Equipment Class: Internally Powered

Patient Connection: Type BF

The Early Bird Bleed Monitoring System (User Interface Display module and introducer sheath) is considered to be the Applied Part.

Electromagnetic Compatibility (EMC)

The Early Bird meets the requirements of IEC 60601-1-2 for a Group 1, Class A device. Specific levels for the Early Bird device appear below.

TABLE 3: Electromagnetic Emissions

Guidance and Manufacturer's Declaration – Electromagnetic Emissions		
The Early Bird is intended for use in the electromagnetic environment specified below. The customer or the user of the Early Bird should assure that it is used in such an environment.		
Emissions Test	**Compliance**	**Electromagnetic Environment - Guidance**
RF Emissions CISPR II	Group 1	The Early Bird uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference to nearby electronic equipment.
RF Emissions CISPR II	Class A	The Early Bird is suitable for use in all establishments other than domestic and those directly connected to the public low-voltage power supply network that supplies buildings used for domestic purposes.

TABLE 4: Electromagnetic Immunity

Guidance and Manufacturer's Declaration – Electromagnetic Immunity			
The Early Bird is intended for use in the electromagnetic environment specified below. The customer or the user of the Early Bird should assure that it is used in such an environment.			
Immunity Test	**IEC 60601 Test Level**	**Compliance**	**Electromagnetic Environment - Guidance**

Electrostatic Discharge IEC 61000-4-2	No false indications, error mode allowed: 8 kV Contact 15 kV Air	Complies	Floors should be wood, concrete or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30 %.
Power frequency (50/60 Hz) magnetic field IEC 61000-4-8	30 A/m 50 or 60 Hz	Complies	If abnormal operation occurs, it may be necessary to position the Early Bird further from sources of power frequency magnetic fields or to install magnetic shielding. The power frequency magnetic field should be measured in the intended location of use to assure that it is sufficiently low.
Conducted RF IEC 61000-4-6	3V 0.15 to 80 MHz 6V in ISM bands between 0.15 and 80 MHz 80% AM at 1 kHz	Refer to TABLE 5	Portable and mobile RF communications equipment should be used no closer to any part of the Early Bird, including cables, than the recommended separation distance calculated from the equation applicable to the frequency of the transmitter. Recommended separation distance d = 1.2 √P 150 kHz to 80 MHz d = 1.2 √P 80 MHz to 800 MHz d = 2.4 √P 800 MHz to 2.5 GHz where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer and d is the recommended separation distance in meters (m). Field strengths from fixed RF transmitters, as determined by an electromagnetic site survey[a], should be less than the compliance level in each frequency range[b].
Radiated RF IEC 61000-4-3	3 V/m 80 MHz to 2.7 GHz 80% AM at 1 kHz	Refer to TABLE 5	

			Interference may occur in the vicinity of equipment marked with the following symbol: 
NOTE 1: These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects, and people.			
[a] Field strengths from fixed transmitters, such as base stations for radio (cellular/cordless) telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered. If the measured field strength in the location in which the Early Bird is used exceeds the applicable RF compliance level above, the Early Bird should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as relocating to an alternate site. [b] Over the frequency range 150 kHz to 80 MHz, field strengths should be less than 3 V/m.			

TABLE 5: Recommended Separation Distances

Recommended separation distances between portable and mobile RF communications equipment and the Early Bird			
The Early Bird is intended for use in an electromagnetic environment in which radiated RF disturbances are controlled. The customer or the user of the Early Bird can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and the Early Bird as recommended below, according to the maximum output power of the communications equipment.			
Rated maximum output power of transmitter	**Separation distance according to frequency of transmitter m**		
	150 kHz to 80 MHz	**80 MHz to 800 MHz**	**800 MHz to 2.5 GHz**

W	d = 1.2 √P	d = 1.2 √P	d = 2.4 √P
0.01	0.12	0.12	0.24
0.1	0.38	0.38	0.76
1	1.2	1.2	2.4
10	3.8	3.8	7.6
100	12	12	24

For transmitters rated at a maximum output power not listed above, the recommended separation distance d in meters (m) can be estimated using the equation applicable to the frequency of the transmitter, where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer.

NOTE 1: At 80 MHz and 800 MHz, the separation distance for the higher frequency range applies.

NOTE 2: These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects, and people.

Impedance Measurement

Applied signal waveform:	10.0 kHz, sinusoidal
Applied signal amplitude:	250 µA peak to peak
Impedance sampling rate:	0.25 seconds
Impedance measurement range:	10 to 95 ohms, -20 to +20 degrees phase

Permissible Environmental Conditions

Temperature:	Transportation and Storage: -29°C to 60°C
Relative Humidity:	Transportation and Storage: 0% to 85%
Atmospheric Pressure:	Transportation and Storage: 50kPa to 106kPa

Operating Conditions: Typical operating room / catheterization laboratory environment

WARNING: No modification of this equipment is allowed.

15. DEVICE RELATED ADVERSE EVENT REPORTING

Any adverse event involving the Saranas Early Bird Bleed Monitoring System should be reported to Saranas, Inc. immediately. To report an event in the United States, please call 713.357.1049, e-mail info@saranas.com, or write to:

Saranas, Inc.
2450 Holcombe Boulevard
Suite X
Houston, TX 77021-2039
USA.

TABLE 6: Symbol Descriptions

SYMBOL	DESCRIPTION
	**Catalog Number**
	**Batch Code**
	**Use by Date**
	**Quantity**
	**Manufacturer**
	**Maximum I.D. (French Size)**
	**Guidewire Compatibility**
	**Do Not Re-use**
	**Do Not Use if Package is Damaged**
	**Keep Dry**
	**Do Not Re-sterilize**
	**Temperature Limit**
	**Humidity Limitation**
	**Atmospheric Pressure Limitation**
	**Consult Electronic Instruction for Use (www.saranas.com/IFU)**
	**Caution**

SYMBOL	DESCRIPTION
	**Keep Away from Sunlight**
	**Caution: U.S. Federal Law restricts the sale, distribution, or use of this device to, by, or on the order of a physician.**
	**Sterilized using Ethylene Oxide**
	**Type BF Applied Part**
IP41	**Ingress Against Water or Particulate Matter (IP) Classification** **Protected against solid foreign objects of 1.0 mm Ø and greater and protection against vertically falling water drops**
RoHS 	**Restriction of Hazardous Substances**
	**General Prohibition Sign, i.e. Do Not…**
	**General Warning Sign, i.e. Caution…**
	**MR Unsafe**