everlinQ Endovascular Access System Enhancements (EASE) Study

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1 INTRODUCTION

End Stage Renal Disease (ESRD) currently affects over 2 million people worldwide.[1] It is projected that the worldwide incidence of ESRD will increase dramatically over the next 10 years, due to the increasing incidence of an aging population, diabetes, hypertension, and obesity.[2] Currently, Renal Replacement Therapy for patients with ESRD consists of either hemodialysis or peritoneal dialysis. The rates of implementation of either hemodialysis or peritoneal dialysis vary widely per country. According to the United States Renal Data System (USRDS), in 2006 hemodialysis accounted for around 60% of Renal Replacement Therapy patients in the US, while peritoneal dialysis accounted for 6- 7% of patients in the US and the remainder is kidney transplant patients.[2]

Vascular access is a critical component in the care of patients undergoing hemodialysis. The three methods of long term vascular access available to a patient requiring hemodialysis are: an autogenous arteriovenous access or native arteriovenous fistula (AVF), a prosthetic arteriovenous graft (AVG) or a tunneled dialysis catheter.[3] The AVF has been shown to be superior to AVG and superior to catheter access in terms of both mortality and morbidity.[4,5] In fact, the focus of numerous initiatives worldwide has been to increase the implementation of AVF as the preferred method of vascular access in patients requiring hemodialysis. In 1997, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines were published to highlight the importance and to promote the increased placement of AVF.[6] These guidelines and subsequent versions have stressed the importance of proactive identification of patients requiring hemodialysis, and have described procedures and quality initiatives to maximize access longevity. In 2006, the updated KDOQI Guidelines recommended that AVF be constructed in at least 65% of prevalent hemodialysis patients.[7] In addition, the AV Fistula First Breakthrough Initiative (FFBI), a coalition lead by the Center for Medicare and Medicaid Services (CMS) has set a formal goal for AVF construction of 65% in prevalent patients by 2009.[8] The Society for Vascular Surgery (SVS) has also approved and sponsored initiatives around the development and publication of reporting standards for hemodialysis access and the development of practice guidelines for hemodialysis access.[9]

An AVF is traditionally created during a surgical procedure under general anesthesia. A surgical incision is made in the forearm or upper arm, followed by identification of target arteries and veins for surgical connection. Frequently, prior to the procedure, the vessels are mapped using duplex ultrasound imaging, allowing for pre-operative vessel diameter measurement and vessel selection. Typically, the radial artery or brachial artery and the cephalic vein or basilic veins are selected. The target vessels are carefully dissected and mobilized, and the vein is transected. An arteriotomy is created, and an anastomosis is sewn between the vein and the artery. After completion, the flow is verified using palpation and ultrasound, and the incision is closed. Over the course of the following 1 - 3 months, the AVF gradually matures, that is, the vein dilates and accepts increased flow sufficient for hemodialysis.

Though there is widespread agreement that the AVF is the preferred method of vascular access, 28 – 60% of AVFs do not successfully mature and are rendered unusable for hemodialysis.[10, 12] This has unintended consequences for patients in immediate need of hemodialysis, since a tunneled dialysis catheter must often be placed. Catheters are associated with higher morbidity, mortality, and costs and are therefore considered a last resort.[11]

To improve on these results, and decrease the invasiveness of the procedure, a new tool and method for creation of an AVF has been developed, called everlinQ system. The system uses two devices,

one inserted into an artery and the other inserted into a closely-positioned vein. The devices contain magnets that bring a pair of electrodes into alignment. Radiofrequency energy is delivered to the electrodes, cutting and/or coagulating the tissue between the electrodes, creating an AVF. The procedure is facilitated using fluoroscopy and ultrasound imaging, to assist in vessel selection and to verify creation of the AVF. Because the vessels are not dissected and not mobilized, leaving the surrounding tissues intact, the vessels do not need to be sewn together with a traditional surgical technique. This proposed method may facilitate the creation of AVF, while reducing the trauma to the patient and also potentially prevent future venous stenosis thought to arise from surgical trauma. In particular, the goal is to reduce the surgical manipulation of the blood vessels, particularly the veins in the arm, which typically exhibit intimal hyperplasia in surgical AVF. Intimal hyperplasia is believed to be a root cause of failure in surgical AVF and AVG, and this technology and method may help improve the patency and maturity of AVF in patients with ESRD.

This clinical pilot study is being conducted to evaluate everlinQ System when utilized to create an AVF.

1.1 Device Description

The TVA Medical everlinQ System that will be used in this study is an investigational device, and is not cleared by FDA or any competent authority for sale in the US or elsewhere.

The everlinQ device is a single-use disposable device. The everlinQ catheter system consists of two flexible, magnetic catheters. One (venous) catheter contains an electrode to deliver radiofrequency (RF) energy, and has a cord that is connected for a remote hand switch. The venous catheter and hand switch, along with a standard grounding pad, connect to a standard electrosurgical unit for the delivery of RF energy. The second (arterial) catheter is a flexible magnetic catheter that contains a backstop for the RF electrode of the venous catheter to interface. Once the catheters are properly inserted and aligned, the magnets contained in each catheter attract to one another, approximating the vessels while simultaneously aligning the electrode with the backstop. RF energy is delivered to the electrode whereby the arterio-venous fistula (AVF) is created.

For additional details regarding device or its principal of operation, please refer to the most current Instruction for Use (IFU).

2 RISKS/BENEFITS

2.1 Benefits

The everlinQ System may facilitate a less-invasive and more reproducible AVF procedure. The everlinQ System may allow the physician to cut and coagulate soft tissues for the creation of an AVF while minimizing surgical incisions. Due to the less-invasive nature of the procedure with the everlinQ System, the AVF may exhibit improved maturation and patency characteristics compared to historical maturation and patency data. In addition, patient recovery time may be decreased, procedural time may be decreased, and anesthesia may be minimized compared to a conventional surgical AVF procedure.

2.2 Risks

Many of the potential risks and complications associated with the everlinQ System and procedure are similar to the risks expected for CKD patients undergoing surgically created arteriovenous fistula (AVF) procedures. The potential risks related to the everlinQ System and procedure are similar to surgical AVF creation and may include but not limited to:

- Bruising
- Numbness, tingling and/or coolness in the fistula extremity
- Occlusion/stenosis (AVF clots)
- Thrombosis (AVF completely clotted and cannot be used)
- Failure to mature (AVF can never be used)
- Additional procedures (interventions)
- Venous hypertension (arm swelling)
- Aborted or longer procedure
- Swelling, irritation or pain
- Bleeding, hematoma (a solid swelling of clotted blood within the tissues) or hemorrhage (an escape of blood from a ruptured blood vessel)
- Wound problem
- Fever (pyrogenic reaction)
- Steal or ischemia (not enough blood flow to hand)
- Embolism (blood clot or device piece)
- Infection (local or in the blood (bacteremia))
- Increased risk of congestive heart failure (heart fails due to increased flow from AVF)
- Vessel, nerve or AVF damage or rupture
- Pseudoaneurysm (leaking hole in artery that forms blood clot on outside of it)
- Heart problems such as arrhythmias (abnormal beats) that can be caused due to high levels of potassium in the blood (mostly due to CKD and not the TVA device or procedure)
- Death (mostly due to CKD related complications not the TVA device or procedure)
- Burns
- Problem due to sedation or anesthesia
- Sepsis (systemic inflammatory reaction)
- Toxic or allergic reaction
- Electrocution

In addition, fistula infiltration injury due to needle cannulation of the fistula is also a known risk/event.

Most of these potential risks also exist for creation of standard (surgical) AVFs. There may also be other risks related to use of the everlinQ System and procedure that are not listed or that are not known at this time. This study will help characterize the adverse events associated with the everlinQ System.

2.3 Minimization of Risk

To minimize the risks, the everlinQ system has undergone pre-clinical testing. In addition, all Investigators participating in this clinical trial will be trained on the everlinQ procedure which will contribute to minimizing risks associated with the use of the device.

3 STUDY METHODOLOGY

3.1 Study Design

This is a prospective, single-center study to evaluate the everlinQ System when used to create an endoAVF in hemodialysis patients. A total of up to 50 subjects will be enrolled and will undergo an endoAVF creation procedure using the everlinQ System. All subjects will be followed for up to 12 months post index procedure based on Investigator's discretion.

3.2 Study Objective

The primary objective of this clinical study is to evaluate the safety and efficacy of using the everlinQ system for the creation of an endovascular AVF (endoAVF) in patients requiring hemodialysis.

3.3 Study Endpoints

Study endpoints will be summarized using descriptive statistics. There are no formal hypothesis tests associated with these endpoints.

- **Technical success:** Verification that an endoAVF has been created and remains patent 1-7 Days after the index procedure. Patency will be determined by experienced examiner as the presence of a bruit that is detected with stethoscope, or presence of thrill, or via Duplex Ultrasound, or via angiogram.

- **Fistula Maturation**: defined as endoAVF that is free of stenosis or thrombosis, with brachial artery flow of at least 500 ml/min and at least 4 mm vein diameter (as measured by duplex ultrasound) OR patient was dialyzed using 2 needles.

- **The Time to Fistula Maturation:** the number of days between the date of AVF creation and the date of endoAVF maturation (based on primary efficacy endpoint definition of maturation)**.**

- **Duration of Central Venous Catheter Exposure:** The rate of CVC use per enrolled subjects at 30-45 Days and other follow-up visits. The analysis will be performed for pre-dialysis and on dialysis patients, as applicable.

- **EndoAVF-related Re-intervention Rate:** The re-intervention rate for endoAVF (defined as any intervention required to maintain or re-establish patency) will be calculated at each available follow-up visit post index procedure.

- **Primary Patency**: The primary patency rate will be determined via Kaplan-Meier methods and based on the time of endoAVF creation until any intervention designed to maintain or reestablish patency or endoAVF abandonment.

- **Secondary Patency:** The secondary patency rate will be determined via Kaplan-Meier methods and based on the time of endoAVF creation until access abandonment. Abandonment due to renal transplant receipt will not be included in this endpoint assessment.

- **Safety:** The safety endpoint is the percentage of patients who experience one or more serious device -related adverse events during the first 3 months following AVF creation.

Additional exploratory analysis:

- Rate of serious procedure-related events will be reported at 3 months.
- Rate of serious device-related event rate will be reported at 3 months.
- Rate of device and/or procedure-related infections at 3 months.
- Arterial and arterialized vein flow rates and diameters will be measured via DUS at 30-45 Days and at each available follow-up visit post index procedure.

3.4 Investigational Site Selection

Investigational site selected to participate in this clinical study will be dependent on the Investigator at the site having the necessary resources to fulfill the clinical research requirements outlined in the protocol. These resources include adequate patient population, facilities and support staff to perform the clinical evaluation according to all applicable requirements.

3.5 Study Population

Candidates for this trial are patients being evaluated for placement of an arteriovenous fistula for chronic hemodialysis. Only patients meeting the inclusion and none of the exclusion criteria who signed Informed Consent Form (ICF) will be enrolled in the study.

3.5.1 Inclusion Criteria

1. Eligible for a native arteriovenous fistula.
2. Adult (age >18 years old).
3. Established, non-reversible kidney failure requiring hemodialysis (including pre-dialysis patients).
4. Target vein diameter(s) ≥ 2.0 mm or large enough to accommodate device diameter.
5. Target artery diameter ≥ 2.0 mm or large enough to accommodate device diameter.
6. Estimated life expectancy > 1 year.
7. Patient is free of clinically significant conditions or illness within 30 days prior to the AV fistula that may compromise the procedure

3.5.2 Exclusion Criteria

1. Known central venous stenosis or central vein narrowing > 50% based on imaging on the same side as the planned AVF creation.
2. Upper extremity venous occlusion(s) and/or vessel abnormality(ies) on the same side as the planned AVF creation that precludes endovascular AVF creation by everlinQ System as deemed by the interventionalists' clinical judgment.
3. Prior surgically created access in the planned treatment location.
4. Functioning surgical access in the planned treatment arm.
5. Pregnant women.
6. New York Heart Association (NYHA) class III or IV heart failure.
7. Hypercoagulable state.
8. Known bleeding diathesis.
9. Immunosuppression, defined as use of immunosuppressive medications used to treat an active condition.
10. Documented history of drug abuse including intravenous drugs within six months of AVF creation.
11. "Planned" concomitant major surgical procedure within 6 months of enrollment or previous major surgery within 30 days of enrollment.
12. Currently being treated with another investigational device or drug.
13. Known allergy to contrast dye which cannot be adequately pre-medicated.

14. Known adverse effects to sedation and/or anesthesia which cannot be adequately pre-medicated.
15. Patients who do not have an ulnar or radial artery.
16. At the time of procedure distance between target artery and vein will not allow magnets to align vessels sufficiently to create the fistula.
17. Evidence of active infections on the day of the index procedure.
18. Written informed consent not obtained.

4 STUDY SCREENING AND FOLLOW-UP PROCEDURES

Patients are required to undergo a thorough screening evaluation prior to the index procedure and return for evaluations according to the study follow-up schedule indicated in Table 1. Study data will be collected on case report forms (CRFs) provided by the Sponsor. Any site's standard of care tests may be done outside of the study (e.g., prior to study participation).

Table 1: Schedule of Study Procedures

Assessment	Screening	Index Procedure	Post Index Procedure				
			1-7 Days	30-45 Days	3 Months	6 Months (Optional)[1]	12 Month (Optional)[1]
Compliance window	-30 days	Day 0	1-7 days	30-45 days	Anniversary date + 14 / -7 days	Anniversary date + 45 / -15 days	Anniversary date + 60 / -30 days
Informed Consent	X						
History, Physical Exam, Laboratory Evaluation	X						
Ultrasound Evaluation	X	X[1]	X	X	X	X[1]	X[1]
Angiography/ Venography	X[1]	X	X[1]	X[1]	X	X[1]	X[1]
Adverse Events		X	X	X	X	X	X
Dialysis Access Data				X[2]	X[2]	X[2]	X[2]

[1] Optional visit at the discretion of the Primary Investigator
[2] Will be obtained after dialysis is initiated using endoAVF created by the everlinQ System.

4.1 Informed Consent

Prior to enrollment, all patients will be informed in detail about the nature of the clinical investigation, as well as its risks, potential benefits, and any anticipated discomforts. All patients must provide written informed consent using Ethics Committee (EC) approved informed consent document.

Proper informed consent should be obtained in accordance with local/country guidelines as needed.

4.2 Screening Evaluation

All patients considered for enrollment must undergo a thorough screening evaluation prior to the scheduled treatment with the everlinQ System. The screening evaluation includes:

- Collection of demographic data;
- A medical history and physical exam;

- A laboratory evaluation (i.e. blood tests); and
- A duplex ultrasound and optional angiography/venography assessment.

There will be a final assessment of the suitability of the patient's study eligibility due to vascular anatomy or other criteria made at the time of the index procedure and thus, there may be some consented subjects who are determined to be ineligible who will not be enrolled in the study.

4.2.1 Duplex Ultrasound

A duplex ultrasound assessment needs to be performed of the flow rates and inner diameters of the arteries and veins of the target vessels based on the training requirements provided for the study.

4.2.2 Angiography/Venography

An optional angiographic or venographic assessment of the suitability of the arteries or veins intended for the endoAVF.

4.3 Index Procedure

If a patient presents for the index procedure with an active localized infection, or other medical condition that precludes treatment at this time, the procedure should be delayed until the infection or medical condition is treated and resolved.

If the Investigator is not an experienced user of the everlinQ System, a Sponsor's representative will be present as needed for procedures at each site to provide technical guidance to the Investigator.

4.4 Follow-Up Visits

See **Table 1** for required and optional follow-up visits.

4.4.1 Unscheduled Visit

In addition to scheduled follow-up visits, the patient should be instructed to contact the Investigator at any time during the follow-up period if he/she has questions or concerns relating to the procedure or the endoAVF. If the patient returns to the clinic for evaluation related to his/her participation in the study, an Unscheduled Visit evaluation should be performed and this data should be recorded on the Follow-Up Visit Case Report Form.

4.4.2 Patient Disposition

The Patient Disposition Case Report Form should be completed whenever a patient exits the study. This includes patients enrolled in the study who:

- complete the study protocol,
- withdraw from the study,
- are lost to follow-up,
- are deceased,
- have other reason(s) for exiting the study.

4.5 Adverse Events

For the purpose of this protocol, an AE will be defined as any adverse medical change (i.e., *de novo* or increased severity in a preexisting condition) from the subject's baseline condition that occurs during the course of the clinical study, after starting treatment, whether considered treatment-related or not. "Treatment" includes all investigative or commercially-approved products administered according to the Study Protocol.

Any pre-planned procedures, interventions, etc. or expected progression of pre-existing conditions (e.g., cancer progression) will not be considered AEs for this study. In addition, normally expected symptoms caused by the treatment are not considered an AE for this study. These may include but are not limited to:

- Transient arterial spasm resolving spontaneously OR with medication only.
- Minor discomfort or bruise at the arterial access place.
- Small amount of bleeding at point of arterial access.
- Transient numbness, tingling or coolness that resolved within 4 weeks post index procedure.
- Bruising at the AVF creation site.
- Side effects of standard-of-care medications.
- Hematoma at the arterial and/or venous access site(s) managed prior to patient discharge and did not adversely affect patient discharge.

Only AEs that are relevant to index procedure, study device, access site or AVF will be collected in the study. For example, if the patient has knee replacement or undergo hysterectomy, these events will be considered as non-study related and will not be required to be recorded via Adverse Event form.

AE Type	Definition
Serious Adverse Event (SAE)	AE that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to foetal distress, foetal death or a congenital abnormality or birth defect NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the Study Protocol, without serious deterioration in health, is not considered a SAE.[13]
Adverse Device Effect (ADE)	AE related to the use of study device. NOTE: This definition includes adverse events resulting from insufficient or inadequate IFU, deployment, installation, or operation, or any malfunction of the study device. This definition includes any event resulting from use error or from intentional misuse of the study device.
Serious ADE (SADE)	ADE that has resulted in any of the consequences characteristic of a SAE
Unanticipated SADE (USADE)	USADE which by its nature, incidence, severity or outcome *has not* been identified in the current version of the study protocol, IFU, or other study documentation.
SUSAR	A SUSAR is suspected unexpected serious adverse reaction
Anticipated SADE (ASADE)	An effect which by its nature, incidence, severity or outcome has been identified in the study documentation.

To classify the event, you may follow the steps below (please refer to additional local requirements as needed).

Is this event:					
1. Serious	Yes			No	
2. Study device or procedure related	Yes		No	Yes	No
3. Unanticipated?	Yes	No			
Event type is →	**USADE or SUSAR**	**ASADE**	**SAE**	**ADE**	**AE (i.e., non-SAE)**

4.5.1 Relationship to Device or Procedure

The investigator will also evaluate the relationship of the adverse event to the everlinQ device or procedure according to the following definitions:

Definite (YES): The AE follows a reasonable timing from treatment (or attempted treatment) with the device and the possibilities of factors other than the device or the index procedure, such as underlying disease, concomitant drugs, or concurrent treatment can be excluded. This includes an AE that occurs during the index (AVF creation) procedure.

Probable (YES): The AE follows a reasonable timing from treatment (or attempted treatment) with the device and the probability of device or procedure involvement cannot be excluded. However, other factors such as underlying disease, concomitant medications, or concurrent treatment may be possible.

Unlikely (NO): The AE follows an unlikely timing relationship from treatment (or attempted treatment) or is more likely due to other factors and there is no definitive information suggesting that it was related to the device or procedure.

Not Related (NO): The AE has no timing relationship from treatment (or attempted treatment) or it can be explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.

The investigator will also evaluate the relationship to the everlinQ portion of the procedure using the yes/no definitions above. The everlinQ portion of the procedure only includes insertion, deployment and removal of the everlinQ catheters.

5 DATA ANALYSIS

Data analysis will be primarily descriptive in nature. Continuous variables, such as age, height, weight, will be summarized by the mean, standard deviation, median, minimum and maximum values. Nominal

variables, such as gender, ethnicity, presence of co-morbid conditions, will be summarized by the number and percentage of subjects within each category defined by the variable. Summary statistics for discrete variables will consist of the number and percent of responses in each category.

6 REGULATORY OBLIGATIONS

6.1 Responsibilities of the EC/EC Approval

The EC has the main responsibility to oversee the welfare of the subjects entered into this study. The EC, by its approval of the informed consent form, also ensures that the potential subjects are aware of the benefits and risk of participation in the study.

Each site must obtain EC approval and any other Regulatory agency's approval as required by local or country guidelines prior to study initiation. A copy of the approval notification and the approved study specific patient informed consent must also be kept on file at the site and a copy provided to Sponsor prior to the enrollment of patients. If applicable, written EC approval of any subject's information materials or any advertisement must also be attained prior to their use.

6.2 Sponsor Obligations

The Sponsor must assume responsibilities that are not limited to the following:

- Provide the Investigator with the necessary information (protocol and IFU) and training required to conduct the investigational study.
- Inform study Investigators of all new information.
- Conduct an evaluation of any USADE and report the result of such evaluation to all reviewing ECs and all participating Investigators within 10 working days of first receiving notice of the event.

6.2.1 Investigator's Documents

The following documents will be provided to the study Sponsor by the Investigator prior to initiation of the study.

- A signed and dated Study Agreement.
- Current (within one year) curriculum vitae of the Principal Investigator and all Co-Investigators.
- A copy of the approval letter by the EC for the study protocol and the informed consent.

6.3 Investigator Obligations

Upon signing the Study Agreement, the Investigator agrees to assume the following responsibilities, to keep the required records, and to file the required reports in a timely manner.

The Investigator agrees to:

- Conduct the investigation in compliance with the signed agreement, study protocol, and applicable regulations. Changes to the protocol will only be made after approval by the sponsor and the reviewing EC, or when necessary to protect the safety, rights or welfare of a subject.
- Conduct the investigation in compliance with the EC and other applicable Regulatory agencies.
- Personally conduct or supervise the investigation.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are

informed about their obligations.

- Protect the rights, safety and welfare of research subjects. All subjects must be informed that the device is being used for investigational purposes.
- Assure initial and continuing review of the investigation by an EC.

6.4 Records and Reports

All records and reports pertaining to this protocol are subject to inspection by regulatory agencies and must be retained for at least two years after the date on which the investigation is terminated or completed or for two years after the date that the records are no longer required for the purpose of supporting an application to regulatory agencies for commercial approval of the therapy/claims, or per local regulations, whichever is later.

6.4.1 Investigator's Reports

The investigator is responsible for the preparation and submission of the reports listed below:

Report	Submitted to	Description
Unanticipated Serious Adverse Device Events and Serious Adverse Device Effects	Sponsor & EC	The investigator's report on any unanticipated serious adverse device event (USADE) or serious adverse device effect (S A D E) must be submitted within 10 working days after the investigator first learns of the event.
Withdrawal of EC approval	Sponsor	The investigator must report a withdrawal of reviewing EC approval within 5 working days.
Deviations from Study Protocol	Sponsor & EC	Notification must be made within 5 working days of the occurrence of an emergency deviation (made to protect the life or physical well-being of a subject). If the deviation affects the rights, safety, or welfare of the subjects (and is not an emergency), or the scientific soundness of the investigation, prior approval must be obtained from Sponsor, the reviewing EC and applicable Regulatory Authorities (when required). For all other deviations, prior approval must be obtained from Sponsor. All deviations must be documented on a Protocol Deviation Form.
Failure to obtain Informed Consent Form	Sponsor & EC	Notification must be made within 5 working days of use of the device.

6.4.2 Sponsor's Reports

Sponsor is responsible for the preparation and submission of the reports listed below:

Report	Submitted to	Description
Unanticipated Serious Adverse Device Effects	EC & Investigators	Sponsor will report on any unanticipated serious adverse device effect evaluation within 10 working days after receiving notice of the effect.
Recall and Device Disposition	EC & Investigators	Notification will be made within 30 working days of Sponsor's request that an investigator return, repair or otherwise dispose of any devices. Such notification will state why the request was made.
Notification of Termination or Completion	EC & Investigators	Notification will be made within 30 working days of completion or termination of the investigation.
Final Report	EC & Investigators	A final report will be submitted within six months after study completion or termination.
Emergency Deviations from Study Protocol	EC	Notification will be made within 5 working days after Sponsor learns of an emergency deviation from the Investigational Plan where the deviation was made to protect the life or physical well-being of a subject.

6.5 Site Training

Sponsor representative(s) will be responsible for site personnel training to ensure that all site personnel have a thorough understanding of the protocol, case report forms and associated study requirements.

A Sponsor's representative(s) will meet with the Investigator at each study site prior to the enrollment of patients for the purpose of reviewing and discussing the protocol and supporting documentation to assure total understanding of the requirements involved in performing the clinical evaluation.

6.6 Protocol Deviations

A Protocol Deviation CRF must be completed for each deviation from the Study Protocol that occurred at the site (e.g., failure to obtain informed consent, enrolling a patient who does not meet inclusion/exclusion criteria, not performing required testing, missed follow-up visits, etc.).

6.7 Site Non-Compliance

Repeated serious protocol deviations will be closely monitored. If excessive deviations or a failure to reduce deviations is noted, the Sponsor reserves the right to suspend study enrollment or terminate the site from the study until a sufficient system is in place at the site to reduce further deviations.

6.8 Device Accountability

A Device Accountability Log (DAL) will be maintained at the study site. Devices allocated for investigational site use will be recorded in the DAL upon delivery to the study site and will be stored in a secured area until use. No devices will be shipped until EC approvals to begin the study are received by the Sponsor. Site personnel will be responsible for tracking the receipt and disposition of all study devices. All unused study devices must be returned to the Sponsor.

The DAL will be updated as each device is used, opened, or returned. The DAL will contain delivery dates of devices to the site, dates used, returned-to-Sponsor dates and the reason for the return, lot numbers of devices delivered to the site, and the patient ID for all used devices.

6.9 Case Report Form Completion

Complete and accurate Case Report Forms (CRFs) must be kept for all patients enrolled in the study. All entries in the CRFs should be made with black or blue ink. There must be an entry for every data point in the CRFs. Corrections to the CRFs should be made by striking out the initial entry with a single horizontal line, with placement of the new entry just above the old. All corrections must be initialed and dated by the person making the correction.

All data collected in the study must be supported by source documentation. Source documentation may include, but not necessarily be limited to: patient medical record notes, patient history questionnaires, physical examination forms, duplex ultrasound data, radiology reports, operative summaries or other documentation that is pertinent to the patient's participation in the study. In addition to existing patient records, a copy of the CRF for the study may be used to directly record study data. If the CRF copy is the only documentation of the collection of study data, the copy should be signed and dated by the Investigator and kept in the patient's record as source documentation.

6.10 Monitoring Procedures

The Sponsor or a Sponsor representative will monitor the progress of the study as required by GCP. The study data will also be monitored (by utilizing remote risk-based monitoring, if feasible). The Sponsor will request the source documents to be submitted to them in de-identified manner (subject's name and other personal identifiers must be removed and replaced with the study subject identification (ID) number). These source documents may include but not limited to:

- Admission, procedural and discharge reports/notes
- Any documentation relevant to SAE and procedure and device-related AEs

Monitoring will be performed by qualified and appropriately trained monitors onsite and/or remote. They may be Sponsor's employees or Sponsor's representatives.

On-site visits may be performed as needed based upon enrollment, data integrity and site compliance (e.g. repeated and serious non-compliance by the site (significant number of DCFs at the site, etc.). Each remote or on-site monitoring visit will be documented.

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