Automated Ultrasound Flow Monitoring for Maturation of Peripheral Arteriovenous Fistulae

Stage 1:
EchoSure Criteria Development and Early Assessment Trial

Stage 2:
EchoSure Fistula Maturation Prediction Trial

Version: May 5, 2019
NCT: NCT04017910

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Protocol Number: [redacted]

Clinical Investigation Plan Version: [redacted]

May 5, 2019

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1. ABBREVIATIONS

AE	Adverse event
CA	Competent authority
CE	Conformité Européene
CEC	Clinical events committee
CRF	Case report form
FDAAA	Food and Drug Administration Amendments Act
GCP	Good clinical practices
ID	Identity Number
IRB	Institutional Review Board
SAE	Serious Adverse Event
SOC	Standard of Care
USADE	Unanticipated Serious Adverse Device

2. PRIMARY STUDY CONTACTS

Sponsor:	David Narrow CEO Sonavex, Inc 2835 O'Donnell Street Suite 200 Baltimore, MD 21224 (443) 862-2024 www.Sonavex.com [redacted]
Investigators:	**Principal Investigator** [redacted]
Study Coordinator:	[redacted]

3. STUDY SUMMARY

Title:	Automated Ultrasound Flow Monitoring for Maturation of Peripheral Arteriovenous Fistulae
Protocol Number:	2019-1
Design:	This is a prospective, single arm, non-randomized, multi-center observational study to demonstrate the performance of the EchoMark and EchoSure devices in patients undergoing peripheral arteriovenous fistula creation for hemodialysis access. **Stage 1:** EchoMark implantation at the time of fistula creation with scheduled follow up for EchoSure imaging of the fistula maturation process. This stage will produce EchoSure criteria for early prediction of maturation failure. **Stage 2:** EchoMark implantation and imaging with EchoSure to prove the robustness of the fistula maturation failure criteria established in stage 1 and measure the effect on ultimate fistula maturation rates.
Study Duration:	Projected enrollment of first patient: May 2020 Projected exit of final patient: December 2021
Primary Objective:	**Stage 1:** The primary objective of the study is to collect data to verify the technology's performance in monitoring fistula maturation and understand the natural history of AV fistula flow physiology. **Stage 2:** The primary objective of the study is to assess the ability of the EchoMark and EchoSure system to reduce the rate of failed fistula maturation.
Patient Population:	Patients undergoing upper extremity autologous arteriovenous fistula creation.
Sample Size:	**Stage 1:** Up to sixty (60) patients will be enrolled. **Stage 2:** Up to sixty (60) patients will be enrolled.
Number of Sites:	To be determined
Treatments: .	**Stage 1:** EchoMark soft tissue marking devices will be placed and monitored using the EchoSure system for 24 weeks or confirmed fistula maturation/failure has been declared by the attending vascular surgeon, whichever comes first. **Stage 1:** EchoMark soft tissue marking devices will be placed and monitored using the EchoSure system for up to 52 weeks. Upon the decision by the attending surgeon that the fistula failure is confirmed or that monitoring is no longer clinically necessary patients will exit the study

Endpoints:	**Stage 1:** • Data collection to verify accuracy • Data collection to understand the natural history of flow physiology in AV fistulas and classify fistulas that will fail **Stage 2:** Primary Performance Endpoints: • Rate of successful fistula maturation Secondary Performance Endpoints: • Cumulative fistula patency at the end of 1 year • Conduit diameter measurements • Volumetric flow measurements

Inclusion Criteria	• Age > 18 years • Patients presenting for upper extremity autologous arteriovenous fistula creation for hemodialysis access where the surgeon selects EchoMark and EchoSure as an appropriate method of monitoring. • Patient is able to sign informed consent and able to participate in all testing associated with this clinical investigation • Women of childbearing potential have a negative pregnancy test.
Exclusion Criteria	• Age <18 years old • Patient unable to sign informed consent • Patient participating in another investigational device or pharmacological study • Prisoner or patient from vulnerable populations as defined in 45 CFR 46.
Follow Up:	Patients will have variable follow up depending on the rate of fistula maturation as well as the follow up required by the surgeon per his or her standard practice.

4. INTRODUCTION, BACKGROUND AND SIGNIFICANCE

Background

Chronic kidney disease (CKD) is overwhelmingly prevalent in the United States: more than one in ten American adults are estimated to have CKD and it is the 9th leading cause of death nationally. Kidney failure, or end stage renal disease (ESRD), is the most severe form of CKD, and its incidence is increasing dramatically; the number of Americans with ESRD has tripled in the last twenty years. The incidence of kidney failure is projected to increase even more because of the aging American population. While the yearly incidence rates for ESRD have increased by about 3% for most age groups, the rate for patients over 75 has grown by 10%. The aging American population has substantial implications for the epidemiology of dialysis; by 2050 a quarter of Americans will be 65 or older. The median age at dialysis initiation is 64, and the peak incidence for ESRD is between 80 and 85. For comparison, by 2020 a quarter of the population will be 65 or older and the number of Americans 85 and older will be around twenty million. The incidence of ESRD is also increasing because of the growing prevalence of comorbid and causative conditions such as hypertension and diabetes, particularly in the elderly population.(2-4)

The health care costs associated with ESRD are substantial. In 2012, the Medicare costs for ESRD, excluding medication, accounted for 7.1% of the total CMS budget. (4) The most expensive modality of renal replacement, hemodialysis, is also the most prevalent. In 2015, hemodialysis cost Medicare $26.7 billion and the expenditure per patient per year was

$88,195.(5) The estimated cost of dialysis between 2001 and 2010 was approximately $1.1 trillion.(4)

Hemodialysis access is a conduit through which dialysis machinery may be connected to the patient's circulatory system. The creation and maintenance of access constitutes a significant portion of dialysis costs. A fifth of all ESRD hospitalizations are attributable to access complications. Current clinical practice guidelines maintain that an autogenous arteriovenous (AV) fistula is the ideal vascular access conduit for hemodialysis (Figure 1).(6) Fistulae are superior to prosthetic grafts insofar as they require fewer interventions to maintain patency, have a far lower rate of failure and infection and a longer usable lifespan. Indwelling central venous catheters have the highest risk of death, infection and cardiovascular morbidity.(7) Autogenous AV fistulae confer a mortality benefit when used for dialysis.(1) In the United States, 63% of patients on dialysis use fistulae.(6)

The primary limitation of AV fistulae is the high rate of failure. Between 30%-70% of fistulae suffer primary failure and are never used because they have failed to mature or adapt into suitable dialysis access.(1) This failure nearly always results in a delay in dialysis initiation and requires placement of a dialysis catheter in addition to another surgery for access creation. The financial burden of a failure to mature is accordingly substantial. Dialysis-related expenses incurred by patients in their first year of renal failure are 23% lower if dialysis is started in a mature fistula than without.(8) Techniques to maximize the rates of maturation hold substantial potential for cost savings. Muray-Cases et al. demonstrated that a program of pre-maturation ultrasonography and intervention resulted in a maturation success rate of 78% at the time of dialysis.(9) Notably, the study involved exclusively distal radiocephalic fistulas, a type that has a typical historical rate of maturation failure between 50-70%.(10) Currently, resource limitations enable reimbursed performance of a Duplex ultrasound if maturation is not present at six weeks. Ultrasound surveillance of the maturing fistula in the early postoperative period is not typically performed as CMS and local coverage determination criteria require clinical indications that cannot apply in the early postoperative period. This 'blind period' immediately after fistula creation holds substantial potential for improvement of care.

Research has established that volumetric flow at six weeks after fistula creation correlates with flow at two weeks after creation.(11) This two-week marker has additional and substantial importance; two weeks postoperatively is accepted as the time at which fistula revision can be performed. Most revision surgeries and procedures do not disturb the primary fistula conduit. Taken together, these represent an opportunity to detect and treat maturation failure as early as two weeks postoperatively and enable a fistula to reach maturation by the expected date. Compared to the abovementioned 30-70% failure rate, regular early ultrasound surveillance has resulted in a success rate of 78%. In 2014 alone, such an improvement would result in the salvage of 25,000 – 70,000 fistulas.(12)

A single imaging modality, ultrasonography, is able to assess volumetric flow within a fistula and determine anatomic factors predisposing it to maturation failure or impending late failure. Duplex ultrasound, however, is a resource-intensive practice that requires the dialysis patient to make an additional visit to an outpatient imaging laboratory and requires a trained, formally certified professional ultrasonographer. The examination itself requires 45 minutes to an hour. It

is only complete after image interpretation by a physician which can take an additional 24-48 hours. The substantial commitment of material resources, time, and personnel make formal Duplex ultrasonography too costly for performance of frequent examination, despite the potential for economic and proven clinical and quality improvement that regular scanning holds.(9)

This potential is not theoretical. Doppler ultrasound imaging has demonstrated utility in predicting both fistula maturity and in detecting impending fistula thrombosis.(1, 9, 11, 13-19) Ultrasound criteria for the prediction of maturation failure have been established, and ultrasound can determine the cause of non-maturation and allow planning for surgical intervention.(1) Studies indicate that routine surveillance of fistulae can predict maturation and that a program of routine ultrasound surveillance decreases the rate of maturation failure significantly.(1, 9, 11, 16) A multicenter study of more than 500 upper extremity fistula creations determined that both fistula diameter and volumetric flow at two weeks postoperatively were significant predictors of successful or unsuccessful maturation at six weeks.(11)

While we have described a 50% decrease in maturation failure as reasonable, at least one study of early postoperative ultrasound for maturation monitoring has shown results surpassing this figure. Muray Cases et al. used early ultrasonography to achieve a 78% maturation success rate. In almost all cases of incipient maturation failure, a single, correctible lesion was identified.(9) Remarkably, because of this early detection not a single patient initiated dialysis with a central venous catheter.(9)

Despite the obvious benefit of ultrasonography to reduce maturation failure, regular surveillance imaging of dialysis access is not routinely performed in the United States. Because of the onerous requirements for high trained technical staff, an interpreting physician, a fully equipped and certified vascular laboratory and the time and effort required to undergo formal ultrasound examination, responsible resource utilization precludes frequent formal scanning. In fact, meeting Medicare criteria for medical necessity for such imaging after the maturation study at six weeks requires documentation of quantifiable access malfunction occurring during dialysis or major clinical findings such as massive upper extremity swelling. This limitation is understandable in light of the economic burden associated with a lengthy Duplex examination of hemodialysis access. Ultrasound assessment of dialysis access entails the cost of a dedicated vascular laboratory, an ultrasound apparatus and a qualified ultrasound technologist. A full examination uses color Doppler imaging, pulsed-wave spectral Doppler imaging, and B-mode ultrasound. The patient burden is equally involved, requiring a separate appointment on an additional delay at a vascular laboratory that may be distant from the patient's dialysis center. The study yields a comprehensive assessment of the fistula and the potential to diagnose conditions ranging from aneurysmal degeneration to medial calcinosis and peripheral ischemia.

Ultrasound surveillance does not require such extensive analysis to benefit maturation and thrombosis rates, however. A single variable – volumetric flow – has been shown effective in predicting both maturation and fistula thrombosis.(9, 13, 17-20) The potential for regular ultrasound surveillance to decrease rates of AV fistula maturation failure and thrombosis does not require complete examinations performed by expert ultrasonographers. This study will use a FDA-approved system for rapid ultrasound assessment of fistula flow during existing patient appointments performed by a clinic nurse, requiring minimal training and equipment.

Surveillance using this method, performed by a clinic nurse in the vascular clinic, will enable realization of that benefit in a way that significantly reduces costs and improves patient outcomes.

Device Description

ECHOMARK
The EchoMark is an echogenic polymeric marker used to mark surgical sites with ultrasound. The device has a specially designed form factor that provides [redacted] when imaged from different angles and positions. EchoMark is produced with a manufacturing technique that enhances acoustic resonance to maximize brightness under ultrasound. EchoMark is composed of a bioresorbable polymer with a long history of use in sutures and medical devices and dissolves within 18-24 months.

ECHOSURE
EchoSure is an FDA-cleared 3D Doppler ultrasound device that automatically delivers visual and quantitative blood flow information, and may be utilized intraoperatively or postoperatively from the bedside by a nurse or other healthcare provider without the need for special sonographic training.

Benefits
EchoMark and EchoSure together enable the patient care team to collect critical blood flow information intraoperatively and during routine patient examinations postoperatively. The technology displays both a visual indication of arterial and venous blood flow in real-time and provides the quantitative changes in volumetric flow rate in each vessel. This information is critical for:

- Identifying fistulae at risk for maturation failure
- Providing key volumetric flow data to guide appropriate intervention for fistula salvage
- Diagnosing potential issues intraoperatively prior to leaving the OR

5. STUDY OBJECTIVES

Purpose

Stage 1: The primary objective of Stage 1 of the study is to collect data to verify the technology's performance in fistula monitoring. In Stage 1, EchoMark is implanted and monitoring is completed post-operatively. EchoSure data is then captured in an effort to establish normal ranges of the relevant variables in the context of appropriately maturing fistulae and their physiology, whis is currently unknown.

Stage 2: The purpose of Stage 2 of the study is to evaluate the performance of the EchoMark and EchoSure (both FDA approved devices) as an ultrasound-based method of monitoring maturation of fistulae. The implant and ultrasound will be used as per IFU. The primary purpose of the study is to collect data on patient outcomes and assess whether or not the information generated from use of

EchoMark and EchoSure can decrease the fistula maturation failure rate and improve the patency of fistulas after up to a year.

Performance Goals

Stage 1:

Primary Performance Endpoint:

- Data collection to verify accuracy
- Data collection to understand the natural history of flow physiology in AV fistulas and classify fistulas that will fail

Primary Safety Endpoint:

- Procedure freedom from Serious Adverse Events (SAEs) during the EchoMark implantation procedure and subsequent post-operative period

Stage 2:

Primary Performance Endpoint:

- Failed fistula maturation rate

Secondary Performance Endpoints:

- Cumulative fistula patency at the end of 1 year
- Volumetric flow data
- Vessel caliber
- Total cost of episode of care

Primary Safety Endpoint:

- Procedure freedom from Serious Adverse Events (SAEs) during the EchoMark implantation procedure and subsequent post-operative care.

6. STUDY DESIGN

This is a prospective, single arm, non-randomized, multi-center observational study to record objective data in patients undergoing upper extremity arteriovenous fistula construction with autologous tissue for the purpose of eventual hemodialysis access, in whom the EchoMark implantable marker is placed at the site of vascular anastomosis and the EchoSure module is used to collect ultrasonic data.

The expected duration of this study will be from May 2020 to December 2021. Patients will be identified and recruited by the surgeons participating in the study, who will be determined at a later date. Patients who have been scheduled for creation of an upper extremity autologous arteriovenous fistula creation surgery will be identified as appropriate for study recruitment. The study details will be explained to identified patients and the consent process will begin for willing patients. Participants in the study will have EchoMark devices implanted at the time of the surgery. Monitoring of fistulae will be performed in the postoperative period. Patients who wish to terminate their participation in the research will no longer receive EchoSure ultrasound examinations of their fistula and will revert to the standard monitoring practice of their surgeon.

Stage 1: Patients will be monitored using the EchoSure ultrasound to collect data. Data will be analyzed in an attempt to formulate normative ranges for relevant variables such that clear, objective metrics consistent with healthy versus pathologic fistula healing are established.

Stage 2: Patients will be monitored via EchoSure ultrasound in addition to the standard of care currently followed by the surgeon. Decisions will be made by the vascular surgeon, using a combination of clinical data and the EchoSure data to determine if and when interventions need to be made to prevent failure of fistula maturation. We will then calculate the effect of the EchoMark and EchoSure on the rate of successful fistula maturation.

With the implantation of any foreign material such as a radiologic marker (EchoMark), there is some risk of infection, inflammation or extrusion. Given the biocompatibility data collected by the company and the extensive prior use of the material in medicine, the probability of such risk is extremely low and has already been evaluated by the FDA during the approval process for EchoMark. There is risk that the ultrasound scan may create mild discomfort for the patient on the wound site. The likelihood and severity of this risk is low. If the patient begins to exhibit signs of infection, inflammation or extrusion, a clinical decision will be made by the team if the risk from the implantable device requires removal of the device. In these cases, the implantable device will be removed, and the patient will be monitored with conventional methods.

If ultrasound scanning is found to create discomfort to patient that exceeds that of traditional monitoring devices such as standard ultrasonography, the patient will be offered the option of discontinuation of EchoSure ultrasound scans and be monitored subsequently with conventional methods.

Despite the significant benefit of fistula surgery, there remains a significant risk of postoperative thrombosis, inappropriate fistula maturation, and continued reliance on prosthetic central vascular access for hemodialysis, all of which can cause serious morbidity and even mortality. By using this technology, it is possible that impending failure of fistula maturation can be detected early enough to salvage the fistula and prevent the impending fistula failure and associated morbidity.

Should the patient opt out of the study, they will be monitored with the current standard of care within the vascular surgeon's practice. This includes clinical observation and color Doppler ultrasonography per the surgeon's standard practice.

7. STUDY POPULATION

Number of Patients

Stage 1: Up to sixty (60) patients will be enrolled and both men and women will

be eligible for inclusion. The estimated enrollment period is six months and patients will be followed until the fistula matures and is suitable for use in dialysis or it is ultimately considered non-salvageable by the vascular surgeon.

Stage 2: Up to sixty (60) patients will be enrolled and both men and women will be eligible for inclusion. The estimated enrollment period is twelve months and patients will be followed until then or the decision by the attending surgeon that the fistula failure is confirmed, or that monitoring is no longer clinically necessary patients will exit the study.

Intended Use

The EchoMark and EchoSure devices are intended to be used by a trained medical professional. The EchoMark device is intended to be a Single Use Device, used in a surgical operating suite or equivalent setting. The EchoSure ultrasound devices are reusable and may be used in the operating suite, a post-operative unit such as the ICU or patient floor, or a typical outpatient clinic. When used intraoperatively or in the presence of breached skin, the ultrasound transducer should be used with a sterile probe cover.

Inclusion Criteria

- Age > 18 years
- Patients presenting for upper extremity arteriovenous fistula construction with autologous tissue for the purpose of eventual hemodialysis access where the surgeon has selected EchoMark and EchoSure as the optimal method of vascular monitoring based on clinical assessment and plan
- Patient is able to sign informed consent and able to participate in all testing associated with this clinical investigation
- Women of childbearing potential have a negative pregnancy test

Exclusion Criteria

- Age <18 years old
- Patient unable to sign informed consent
- Patient participating in another investigational device or pharmacological study
- Prisoner or patient from vulnerable populations as defined in 45 CFR 46.

This study will not target the recruitment of any potentially vulnerable subjects. If vulnerable subjects who are educationally or economically impaired present for fistula creation, they will not be given the opportunity to participate in the study.

PATIENT WITHDRAWAL FROM THE STUDY

Patients are free to withdraw consent at any time. Patients who wish to terminate their participation in the research will no longer receive EchoSure ultrasound examinations of their fistula and their data will be removed from the study.

8: STATISTICAL ANALYSIS

Stage 1:
We will recruit 60 patients for participation in this study who are planning to undergo elective construction of upper extremity autogenous hemodialysis access. The minimum sample size of 45 was determined assuming a 50% successful fistula maturation rate (based on past studies) to yield sufficient power to detect a difference in maturation between this cohort and the intervention cohort in the next aim. It also accounts for the quantity of patient volumes needed to develop a [redacted] based on our experience with EchoSure. Lastly, this provides sufficient power to detect a difference in fistula maturation success based on the flow rate (logistic regression power estimation; $\alpha = 0.05$, $\beta = 0.8$, OR 2.5 [from Pr(H0) 0.45 and Pr(H1) = 0.65]. As a buffer, based on institutional experience with clinical research and subject attrition a drop-out rate of 25% has been added to yield a total of 60 patients.

Using the EchoSure-derived conduit diameter and volumetric flow as observed values and Duplex-derived conduit diameter and volumetric flow as accepted values, the accuracy of EchoSure will be calculated. Logistic regression will be used to assess the correlation between successful maturation and EchoSure-derived values for flow and conduit diameter at two weeks. Cut points will be evaluated to establish EchoSure criteria for [redacted]. Pearson's correlation will be performed on both EchoSure-derived and Duplex-derived values of volumetric flow and conduit diameter to determine correlation between EchoSure findings at two weeks and both EchoSure and Duplex findings at six weeks.

Stage 2:
For this portion of the study, we will recruit an additional 60 patients planning to undergo elective construction of upper extremity autogenous hemodialysis access. Again, the EchoMark fiducial marker will be inset at the time of fistula creation. The minimum sample size of 45 (60 prior to 25% dropout factor) is powered to detect an approximate 25% reduction in all-cause fistula failure in the early postoperative period. A $\chi 2$ power analysis was performed with $\alpha = 0.05$, $\beta = 0.8$ and standard-of-care fistula maturation success at 50% based on institutional experience and prior literature which ranges from 30-70% and EchoSure early intervention success based on the Muray-Cases results which showed a 78% success rate achieved by a novel program of pre-maturation ultrasonography and early intervention.

The nominal-by-interval association coefficient, Eta, will be calculated to determine the correlation between successful, unassisted maturation and EchoSure-derived values for flow and conduit diameter at two weeks. This will be compared to the similar findings of stage 1 using Student's t-testing and will validate the early maturation criteria derived from there. The association coefficient will be calculated to determine the correlation between successful, assisted maturation and EchoSure-derived values for flow and conduit diameter immediately following intervention. Pearson's correlation will be performed on both EchoSure-derived and Duplex-derived values of volumetric flow and conduit diameter to determine correlation between findings immediately following intervention and those at six weeks. [redacted]

Using $\chi 2$ testing between the stage 1 and 2 cohorts, the benefit to maturation success of intervention based on early postoperative EchoSure examination will be determined.

9: PATIENT ENROLLMENT AND CONSENT

Method of Subject Identification and Recruitment
Patients will be identified and recruited by the surgeons participating in the study. Patients who have been scheduled for a fistula creation surgery will be identified as appropriate for study recruitment. The study details will be explained to identified patients and the consent process will begin for willing patients.

Informed Consent
Written informed consent, in accordance with applicable international standards and trial center regulations, shall be obtained from each subject, prior to the trial procedures. The investigator retains a copy of the signed informed consent document in each subject's record, and provides a copy to the subject.

The Investigator must obtain the written informed consent of all subjects, and must not allow any subject to participate in the investigation prior to obtaining governing institutional review board (IRB), research ethics board (REB) approval, or Ethics Committee (EC) approval. Before starting the trial, the investigator provides the trial Sponsor with a copy of the sample Informed Consent document approved by the IRB, REB, or EC with documented evidence that the IRB, REB, or EC approved the protocol and the informed consent.

Process of Consent
Patients eligible for the study will receive detailed written information on the trial, after which they will be asked to give *written* informed consent in accordance with the local clinical site's Ethics Committee. ***Oral consent is not an acceptable substitute***.

Consent may only be obtained in person by a member of the study team delegated with consenting responsibilities. Consent will be obtained by a member of the research team in the patient's preoperative visit to clinic or in the pre-operative area prior to the initiation of anesthesia. The research team will take as much time as necessary to confirm full understanding of the study in the consent discussion. There will be sufficient time for the patient to consider the

study obligations and decide whether or not to participate, as study participation will not change clinical care and their data can be removed at any time if they choose to disenroll. Participation is fully optional.

Study personnel should explain that even if a patient agrees to participate in the study and signs the ICF, the patient may not be eligible to participate if he/she fails additional eligibility criteria or the surgical plans changes during the procedure.

Once signed, a copy of the Patient Informed Consent document and the Patient Information Sheet will be given to the patient.

A Screening and Enrollment Log will be maintained in the on-site clinical records located at the study site to document select information about candidates who are enrolled in the study as well as those who fail to meet the entry criteria.

Vulnerable Subjects
This study will not specifically target the recruitment of any potentially vulnerable subjects. If a patient from a vulnerable population presents for a fistula creation procedure, they will not be given the option to participate in the study.

Study Enrollment
Patients will be considered enrolled in the trial once informed consent has been obtained and all eligibility criteria confirmed.

10. STUDY PROCEDURES AND METHODS

Patients undergoing fistula creation procedures will be identified. The study will be explained to these patients and informed consent for participation in the study will be obtained from willing patients. A small, FDA-approved tissue marker will be implanted prior to closure of wounds following the Instructions for Use on the FDA-approved labelling.

Stage 1: The fistula will be assessed with intermittent EchoSure examinations, sometimes during routine dialysis visits (maximum 3x/week) to minimize travel. This will conclude when the fistula has entirely matured and the patient begins hemodialysis via the fistula or when the vascular surgeon declares that the fistula has failed despite any and all salvage attempts.

Stage 2: Similar to stage 1 but with implementation of the normative values for relevant variables that resulted from the data collected in stage 1, with subsequent use of the EchoSure flow information in the vascular surgeon's decision making. This stage will also conclude when a year has passed and the fistula is functioning or when the vascular surgeon declares that the fistula has failed despite any and all salvage attempts or that monitoring is no longer clinically necessary.

Actions to Be Taken by Site Staff	Screening and pre-operative evaluation	Clinic Visits	Initiation of dialysis or fistula failure
Consenting	X		
Initial Enrollment Form		X	
Nurse Scan Form		X	
EchoSure Scan		X	
Standard Clinical Exam		X	
End of Trial Period Form			X

11: DATA COLLECTION, ANALYSIS, AND MONITORING

Adverse events are not expected in this study. Unanticipated problems will be reported and discussed with the principal investigator and research coordinator. Patients will be regularly monitored for signs of infection, inflammation or device extrusion. Should the implantable device require removal, it will be removed, and patient will be monitored with conventional methods. The research team will periodically review its protocols to ensure maximal patient safety and data validity.

Source Documentation

The Investigator must maintain complete source documents on all trial patients who are enrolled in the trial or who undergo screening. Source documents include patient medical records, hospital charts, clinic charts, Investigator's patient trial files, as well as the results of diagnostic tests (e.g., laboratory tests) kept in an individual patient binder and stored in a secured and locked location and must be made available to the sponsor or designated monitor during site visits.

The following minimum information should be recorded in the patient's medical records:

- The date the patient entered the trial and the patient number
- The trial protocol number and the name of the Sponsor
- The date that informed consent was obtained
- Evidence that the patient meets trial eligibility requirements (e.g., medical history, trial procedures and/or evaluations)
- The dates of all trial related patient visits
- Evidence that required procedures and/or evaluations were completed
- Documentation of specific device used, if any
- Occurrence and status of any Adverse Events
- The date the patient exited the trial, and a notation as to whether the patient completed the trial or was discontinued, including the reason for discontinuation

DATA QUALITY ASSURANCE

Case Report Forms specific to the trial will be used for the collection and recording of data at the Investigational site. Investigators are responsible for the timely completion and storage of these forms.

All CRFs will be collected by the Investigator and entered into a database. All case report forms received will be reviewed, tracked and filed. Prior to data entry, a pre-entry review will be conducted to ensure that mandatory fields have been completed. Incoming data will be reviewed to identify inconsistent or missing data. All hard copy forms and data files will be secured to ensure confidentiality.

Investigators are to maintain all source documents, including diagnostic test reports, laboratory results, completed case report forms, supporting medical records and informed consent. The source documents will be referenced during monitoring visits to verify the information documented on the case report forms.

Only clinicians involved in the study will have access to the data. All data will be collected electronically through the medical record system. Access to source documents will be per respective EHR guidelines on computers that are encrypted and password protected. HIPAA compliance guidelines will be used at all time. Human subjects will not be directly identifiable, but only identifiable in the study database through identifying information (Hospital, MRN). The study data will be saved on a HIPAA compliant secure cloud service.

PATIENT CONFIDENTIALITY

All information concerning patients or their participation in this trial will be considered confidential. Only authorized Sonavex personnel and designated consultants and regulatory agencies will have access to these confidential files. Enrolled patients will be assigned a unique identifier that will be used to maintain confidentiality of each patient's medical information. Patient names and other protected health information will not be captured on the case report forms.

12: ETHICS

IRB approval will be sought from CPHS (Committee For the Protection of Human Subjects) for this study.

An individual knowledgeable about the study, likely a listed member of the study personnel, will obtain consent in person from individuals involved in this study. Consent will likely be obtained in clinic or in the pre-operative area prior to the initiation of anesthesia. The team will take as much time as necessary to confirm full understanding of the study in the consent discussion. There will be sufficient time for the patient to consider the study obligations and decide whether or not to participate. Participation will be fully optional.

13: REFERENCES

14: ATTACHMENTS

1. Consent Document

14.1: CONSENT DOCUMENT

Attached as separate document