Observational Study of Outcomes after EchoMark and EchoSure-based Free Flap Monitoring

Protocol Number: 2019-1

Clinical Investigation Plan
Version: 1.1

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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

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Principal Investigator(s)	[redacted] *Protocol Signature pages are provided separate to this protocol*

3. STUDY SUMMARY

Title:	Observational Study of Outcomes after EchoMark and EchoSure-based Free Flap Monitoring
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 free flap surgery.
Study Duration:	Projected enrollment of first patient: March 2019 Projected exit of final patient: November 2019
Primary Objective:	The primary objective of the study is collect data on patient outcomes in cases where the surgeon has chosen it as the appropriate method of monitoring.
Patient Population:	Patients undergoing free flap surgery.
Sample Size:	Up to four hundred (400) patients will be enrolled.
Number of Sites:	Up to eight (8) sites.
Treatments:	One or two EchoMark soft tissue marking devices will be placed and monitored using the EchoSure system for 72 hours.
Endpoints:	**Primary Performance Endpoints**: • Surgeon evaluation of improved monitoring ability and satisfaction **Secondary Performance Endpoints:** • Flap failure rate • Flap takeback rate • Flap salvage rate • Total cost of hospitalization • Time from OR departure to return to OR • Nurse evaluation of improved monitoring
NCT Number	03915717

Inclusion Criteria	• Age ≥ 18 years • Patients presenting for microvascular tissue transfer procedures 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 no follow-up responsibilities following their discharge from the index surgical procedure.

4. INTRODUCTION, BACKGROUND AND SIGNIFICANCE

Background

In free flap surgery (microvascular tissue transfer procedures) blood flow to the skin and soft tissue is critical to tissue survival and wound healing. Compromised blood flow can lead to necrosis, wound break down, delayed wound healing, and wound infection. If blood flow to skin and soft tissue is not maintained, tissue death occurs. Therefore, blood flow into the tissue is of utmost importance in free flap surgery. Because any compromised blood flow could lead to tissue death if not detected early, we routinely monitor patients in hopes of detecting vascular compromise while reperfusion and tissue salvage remains a possibility.

Currently, we rely on several methods to monitor flaps as no satisfactory solution exists. We inspect all flaps for color, warmth, and capillary refill. We have tried some of the existing monitoring devices, such as transcutaneous Doppler, implantable Doppler or near infrared spectroscopy. These systems each have their drawbacks, which include false positives and late detection of a problem. For example, current transcutaneous Doppler systems can be inaccurate and reflect the flow of blood through a vessel other than at the surgical site of interest. Inspection is subjective and can be examiner dependent. In some cases, our flaps our buried beneath the skin and visual inspection is not an option. For these reasons, we are interested in continuing to evaluate potential methods for improved flap monitoring. The Sonavex EchoMark is an FDA approved device that is highly echogenic to provide clear marking of the at-risk vessels such that the surgical site can be easily monitored. The Sonavex EchoSure is a color Doppler ultrasound device for monitoring blood flow. The technology provides clinicians with a clear and reliable assessment of blood flow into and out from the free flap to assess the viability of the tissue. We hypothesize that this technology could be used to detect early tissue compromise, predict tissue death, and potentially allow for early intervention. If this system allows detection of tissue compromise, it would improve wound dealing, decrease skin necrosis or flap death, and improve

patient safety and outcomes. Of note, Doppler ultrasound has already been used to monitor flaps [Rosenberg JJ, Fornage BD, and Chevray PM 2006 Monitoring Buried Free Flaps: Limitations of the Implantable Doppler and Use of Color Duplex Sonography as a Confirmatory Test, Vakharia KT, Henstrom D, Lindsay R, Cunnane MB, Cheney M, and Hadlock T 2012 Color Doppler Ultrasound: Effective Monitoring of the Buried Free Flap in Facial Reanimation]. However, there is little comparative data versus other methods of monitoring. This study is primarily aimed at collecting data assessing the performance of Doppler ultrasound monitoring with EchoMark in a more quantitative way.

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 intuitive, continuous changes in its two-dimensional ultrasound outline 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 a 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:

- Detecting vascular compromise early enough for flap salvage
- Delivering reliable information to eliminate false positives and unnecessary take-backs to the OR
- Selecting optimal vessels for free flap surgery, and
- Diagnosing potential issues intraoperatively prior to leaving the OR

5. STUDY OBJECTIVES

Purpose
The purpose of this study is to evaluate the performance of the EchoMark and EchoSure (both FDA approved devices) as an ultrasound-based method of monitoring the viability of free flaps and patency of at-risk vessels. The implant and ultrasound will be used per IFU. The primary purpose of the study is to collect data on patient outcomes in cases where the surgeon has chosen it as the appropriate method of monitoring.

Performance Goals

Primary Performance Endpoint:

- Surgeon evaluation of improved monitoring ability and satisfaction

Secondary Performance Endpoints:

- Flap failure rate
- Flap takeback rate
- Flap salvage rate
- Total cost of hospitalization
- Time from OR departure to return to OR
- Nurse evaluation of improved monitoring

Safety Goals

Primary Safety Endpoint:

- Procedure freedom from Serious Adverse Events (SAEs) during the EchoMark implantation procedure, hospitalization, and at discharge.

6. STUDY DESIGN

This is a prospective, single arm, non-randomized, multi-center observational study to record subjective and objective data in patients undergoing free flap surgery where the surgeon has chosen to use the EchoMark and EchoSure devices for flap monitoring.

7. STUDY POPULATION

Number of Patients

Up to four hundred (400) patients will be enrolled and both men and women will be eligible for inclusion. The estimated enrollment period is nine months and patients will be followed until discharge from their index surgical procedure.

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 device is reusable and may be used in the operating suite or a post-operative unit such as the ICU or patient floor. When used intraoperatively or in the presence of breached skin, the EchoSure Probe should be used with a sterile probe cover.

Inclusion Criteria

- Age ≥ 18 years

- Patients presenting for microvascular tissue transfer procedures 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.

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 ultrasound examinations of their free flap and their data will be removed from the study.

8: STATISTICAL ANALYSIS

Statistical power was calculated based on determination of the number of detected thrombosis events needed to see a difference between EchoSure and an alternate method of flap monitoring (e.g., clinical examination). A one-tailed paired t-test was used to compare the dichotomous outcome of whether EchoSure detected a thrombotic event prior to other methods of monitoring. At α=0.05 and β=0.80 with a medium Cohen's effect size of 0.5, 27 thrombotic events are needed for comparison. With a baseline national re-exploration rate of about 7%, an enrollment of 385 patients will provide sufficient sample size for the analysis.

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 free flap 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 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. Due to the low risk of the study, if a patient from a vulnerable population presents for flap procedures, they will be given the option to participate in the study.

Study Enrollment

Patients will be considered enrolled in the Observational Study of Outcomes after EchoMark and EchoSure-based Free Flap Monitoring trial once informed consent has been obtained and all eligibility criteria confirmed.

10. STUDY PROCEDURES AND METHODS

Patients undergoing free flap procedures will be identified. No additional clinic visits or additional hospital stay will be required of any study participant. All monitoring of skin or soft tissue will be carried out in the same manner. EchoMark will be implanted prior to closing the patient following the Instructions for Use on the FDA-approved labelling.

The flap will be non-invasively monitored with the EchoSure ultrasound intraoperatively and postoperatively. Intermittent ultrasound monitoring will be performed postoperatively at the institutional standard flap check protocol (q1 hours in first 24 hours, q2 hours in hours 24-48, and q4 hours thereafter) until the patient is discharged from the hospital. Presence of arterial and venous flow will be recorded. Images and/or video clips will be saved.

Actions to Be Taken by Site Staff	Screening and pre-operative evaluation	Surgery Date	Each Scan	Discharge
Consenting	X			
Initial Enrollment Form		X		
Nurse Scan Form		X	X	
EchoSure Scan			X	
Standard Clinical Exam			X	
End of Trial Period Form				X

11: DATA COLLECTION, ANALYSIS, AND MONITORING

Participating surgeons and nurses will complete a brief survey (see CRFs in appendix) capturing their assessment of whether they felt EchoMark and EchoSure improved their ability to monitor free flaps. Surgeons will complete a short form detailing the clinical characteristics and outcome of the case (e.g., whether there was a vascular flow problem and how it was detected). This, and the data management and storage, will be managed by the PI.

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 Observational Study of Outcomes after EchoMark and EchoSure-based Free Flap Monitoring 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.

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.