Evaluation of longer duration use of the SAVI SCOUT Surgical Guidance System for Excision of Breast and Axillary Lesions in Neo-adjuvant Therapy Patients: A Pilot Study

Short Title:
SAVI SCOUT Time Pilot Study

IRB Protocol Number:
MH#2016.078

Principal Investigator:
Mary K. Hayes, M.D.

Co-Investigators:
Erica Bloomquist, M.D.,
Surgeon
Heather Wright, M.D.
Surgeon
Aeisha Rivers, M.D.
Surgeon
Marcelo Blaya, M.D.
Oncologist
Mayra Frau-Reyna, M.D.
Radiologist
Rakesh Parbhu, M.D.
Radiologist
Jessica Batista, M.D.
Radiologist

Lead Institution:
Memorial Regional Hospital
(Hollywood, FL)

Sponsor:
Cianna Medical, Inc. (Aliso Viejo, CA)

Protocol Version Number: 1.4
Protocol Date: December 262018

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice (ICH E6) and the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46) and the Memorial Healthcare policies and procedures pertaining to research involving human subjects or review of patient records. All personnel involved in the conduct of this study have completed human subject research training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name: Mary K. Hayes, M.D.

Title: Chief, Women's Imaging, Radiology Associates of Hollywood, Inc.

TABLE OF CONTENT

LIST OF ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
CT	Computed Tomography
CFR	Code of Federal Regulation
pCR	complete pathologic response
FDA	Food and Drug Administration
FTV	Functional Tumor Volume
HIPAA	Health Insurance Portability and Accountability Act
IFU	Indication for Use
IRB	Institutional Review Board
MHS	Memorial Healthcare System
MR	Magnetic Resonance
NACT	Neoadjuvant Chemotherapy
NAT	Neoadjuvant Treatment
NSR	Nonsignificant Risk
OHR	Office of Human Research
PHI	Protected Health Information
PI	Principal Investigator
RCB	Residual Cancer Burden
RFS	Recurrence Free Survival
SAE	Serious Adverse Event
SCOUT	SAVI SCOUT Device (Cianna Medical, Inc.)
UADE	Unanticipated Adverse Device Event

PROTOCOL SUMMARY

Title: Evaluation of longer duration use of the SAVI SCOUT Surgical Guidance System for Excision of Breast and Axillary Lesions in Neo-adjuvant Therapy Patients: A Pilot Study

Purpose: The purpose of this study is to evaluate the performance of FDA cleared SAVI SCOUT Breast Localization and Surgical Guidance System (SCOUT) over a longer duration prior to surgery. The device(s) is a non-wire system, which uses nonradioactive light-activated radar, to provide breast surgeons with real-time guidance to locate and remove the target lesion(s) in the breast and/or axillary tissue.

The SCOUT device standard of care use is placement up to 365 days prior to surgery to assist surgeons in the localization and retrieval of breast/axillary lesions. Routine image-guided methods (Mammography, Ultrasound, and CT) are used. In this study, we will assess the longer term placement of 1 – 4 SCOUT devices over an extended time (31 - 365 days) in order to address the needs of patients who require neoadjuvant treatment prior to definitive surgery.

Hypothesis: Placement of the SCOUT device(s) prior to neoadjuvant treatment with biologic (hormonal) and/or chemotherapy allows for long-term localization of breast/axillary lesions targeted for surgical excision.

Objectives: Main Objective: To show that the SCOUT device(s) can be used over an extended time (up to 365 days) prior to surgery to successfully guide surgical excision of breast or axillary lesions in patients who undergo neoadjuvant therapy.

Primary Endpoint:

The primary endpoint of this study is successful surgery. Successful surgery (defined as one where the device stays in place and can be removed successfully during surgery) when this device(s) is placed 31 - 365 days prior to surgery. Unsuccessful surgery is defined as one where the device(s) does not stay in place and/or cannot be removed successfully during surgery) when this device(s) is placed 31 - 365 days prior to surgery.

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Secondary Endpoints:

- Number of days prior to surgery (31 - 365) that the SCOUT device(s) is placed by the radiologist to localize the target breast / axillary tissue.
- Success rate of device(s) placement by radiologist (within 1 cm of the center of the target tissue).
- Success rate of SCOUT localization procedure(s) stability. The SCOUT(s) should

not migrate more than 5 mm between day 0 - 365 days pre-surgery. This is measured on routine mammogram and/or ultrasound.
- Rate of device-related complications.
- The number of additional localization procedures needed to supplement the initial SCOUT(s) standard of care localization procedure(s).

Population: The study population consists of 25 - 35 adult surgical patient volunteers who plan to have definitive breast cancer surgery at Memorial Healthcare System (MHS) Hospitals after neoadjuvant treatment.

Phase: N/A

Number of Sites: 3, listed below:

1. Memorial Regional Hospital
   3501 Johnson Street
   Hollywood, FL 33021

2. Memorial Hospital West
   703 N Flamingo Road
   Pembroke Pines, FL 33028

3. Memorial Hospital Miramar
   1901 SW 172nd Avenue
   Miramar, FL 33029

Description of Intervention: Using Radiology standard of care imaging guidance, (Mammography, Ultrasound or CT) the SCOUT device(s) will be placed percutaneously 31 - 365 days prior to the scheduled surgical excisional procedure(s).

During the surgical procedure, the SCOUT system will be used to locate and excise the device and target tissue.

Study Duration: Approximately 25 months. Accrual of 25 - 35 patients (total) from MHS will occur within 12 months. Final data analysis will be completed within 1 month after the last patient is treated. Interim subject accrual will be evaluated after 3, 6, 9 months.

Subject Participation Duration: 1 month – 13 months.

Estimated Time to Complete Enrollment: 6 – 12 months.

Schematic of Study Design:

Patient has SAVI SCOUT LOCALIZATION by Radiologist at any time prior to neoadjuvant treatment
SAVI SCOUT placed anytime ***FDA clearance 10/31/17***

Study Visit 1

ELIGIBILITY and CONSENT and ENROLLMENT

Research Surgeon/MCI Research Nurse/ Investigator

Subject meets Inclusion/Exclusion Eligibility
Informed Consent: Before or after SAVI SCOUT LOCALIZATION and PRIOR TO NACT
Documentation of Consenting Process Form

Research Radiologist
Completes Device Placement Form
Assigns Study ID
Copy of Consent and Study ID sent to OHR for tracking.

Sometimes, additional studies ordered by Med-Onc can impact surgical plan.

Neoadjuvant treatment begins.

**Breast Radiologist performs standard of care pre-operative skin marking*

Study Visit 2
(Day up to 30 prior to surgery)

Research Radiologist
Completes Device Placement Recheck [Device Placement Form] on standard of care imaging and performs audio verification and repeat skin marking if requested as standard of care by surgeon.

Research Surgeon
Excision (standard of care) performed by Research Surgeon
Device Surgical Excision Form

Study Visit 3
(Day of surgery + 30 days)

Research Radiologist completes:
Study Completion Form
ALL Unanticipated Adverse Device Events (UADE) Form

**Note distinction of Breast Radiologist (standard of care SCOUT) vs. Research Radiologist (who Completes Forms)*

1. KEY ROLES and contact information:

Principal Investigator:

Mary K. Hayes, M.D.
Chief, Women's Imaging Center
Radiology Associates of Hollywood, Inc.
Memorial Regional Hospital
3501 Johnson Street
Hollywood, FL 33021

Phone: 954-265-6311
mhayes@mhs.net

Institutions: Memorial Healthcare System Women's Imaging Centers:

Memorial Regional Hospital
3501 Johnson Street
Hollywood, FL 33021

Memorial Hospital West
703 N Flamingo Road
Pembroke Pines, FL 33028

Memorial Hospital Miramar
1901 SW 172$_{nd}$ Avenue
Miramar, Fl 33029

Key Personnel: **Data Manager:** Mary Hayes, M.D.

2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE:

2.1 Description of the SAVI SCOUT Breast Localization and Surgical Guidance System

The SAVI SCOUT Surgical Guidance System (SAVI SCOUT, Cianna Medical, Inc.) is an FDA cleared medical device that aids in the surgical excision of breast lesions without the use of wires or radioactive materials. The system employs nonradioactive light-activated radar SCOUT device, which is placed in breast or axillary lesions under imaging guidance up to 365 days prior to surgery, to guide the surgical excision of non-palpable lesions (Standard of Care).

The system consists of the SCOUT (device) and two major components:

1. A localization SCOUT (device) is placed, percutaneously via a 16-gauge needle at the breast/axillary lymph node lesion. The device uses light (radar) technology to activate an audio and numeric signal to aid the surgeon to locate the target tissue. The device contains nitinol wire, which is a standard medical material composed of nickel and titanium. After placement, the device is safe and visible under all standard imaging modalities (Mammogram, Ultrasound, CT, PET-CT, X-ray, and MRI).
2. A handpiece (PROBE) is used by the surgeon intra-operatively. In the operating room, the sterile PROBE is connected to the console and is placed in direct contact with the skin or within breast/axillary tissue to send /receive the audio and numeric signal to guide the surgeon.

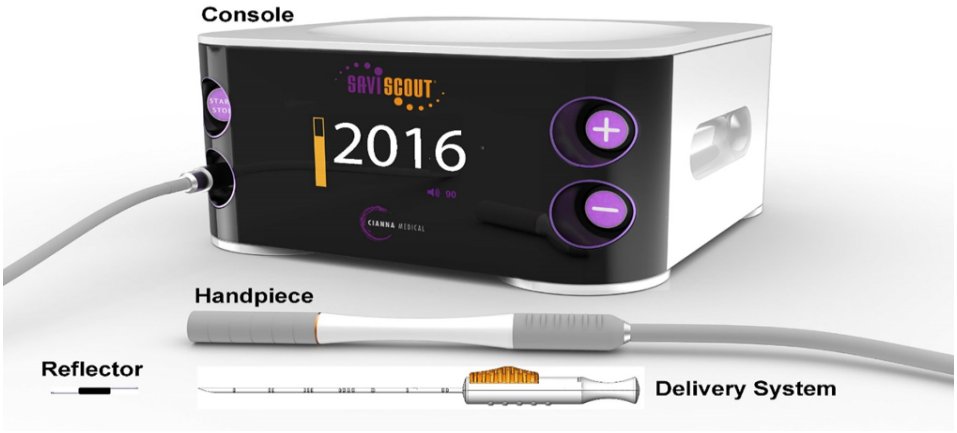

Figure 1. SCOUT System Components

2.2 Rationale

The SAVI SCOUT (Cianna Medical, Inc.) surgical guidance system received 510(k) U.S. Food and Drug Administration (FDA) approval in August 2014 (1). FDA clearance for long-term use was approved in October 2017 (2).This system is currently used as standard of care since 2015 in the MHS operating rooms by experienced breast surgeons (over 600 MHS breast cancer patients and over 28,000 U.S. breast cancer patients as of September 2016) (3, 5). MHS standard of care practice, the device(s) is placed at the target lesion(s) under image-guidance by the radiologist up to 365 days prior to surgery.

Patients with certain types of breast cancer undergo neoadjuvant treatment with biologic (hormonal) and/or chemotherapy with the goal of decreasing the tumor volume prior to definitive surgery. If the original cancer lesion(s) resolve completely, this is called complete pathologic response (pCR) (4). pCR and even a partial response, while good for the patient, can result in disappearance or poor visualization of the target and often render pre-operative image-guided localization by the radiologist more difficult and less reliable. This can result in unintended larger, more disfiguring breast cancer surgery. Therefore, if the SCOUT device(s) can be placed prior to treatment response, when the lesion(s) is clearly visualized on imaging, accurate image-guided targeting is optimal and thus placement and subsequent surgery should be more accurate. If this pilot study demonstrates successful performance of the device without device-related complications, it will bring improved value to future patients who will require fewer and/or less extensive pre-operative and surgical procedures. Some value may also be provided to subjects as the targeting before tumor shrinkage is expected to be more accurate.

During the excisional procedure, the surgeon uses the console and PROBE to locate the SCOUT device(s) and breast and/or axillary tissue for targeted excision.

This pilot study will assess the performance of FDA cleared SCOUT system over a longer duration prior to breast and/or axillary lymph node surgery.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The risks of SCOUT localization are similar to or less than wire localization: bleeding, injury to vessels, adjacent tissue injury, pain, infection and repeating the procedure.

The most significant risk for this study is if the surgeon may not be able to successfully excise the device and/or target lesion. This has not occurred to date in our clinical (>150 patients) experience at MHS with our experienced breast surgeons.

Another potential risk to the patients is that the SCOUT device(s) might move during the 31 -365 day time period. This could possibly require a longer procedure to remove the lesion(s) and/or retrieve the device(s). This has occurred to date in our clinical experience in less than

1% of our initial 150 patients, which is less than the device risk of wire migration (2 - 3%) which has been reported in the US for over 30 years.
Furthermore, standard wire localization procedures may require a second surgery to re-excise and get clear margins. Standard wire localization re-excision rate is reported by the American Society of Breast Surgeons as 20 - 40% nationally .However, the rate of positive margins with SCOUT localization is non-inferior or better than wire localization (1).

2.3.2 Potential Benefits

If long-term SCOUT device(s) localization is successful, neo-adjuvant therapy patients should be able to avoid some of the common and costly limitations associated with standard localization. After neo-adjuvant therapy, lesions are incompletely visualized for targeting. This can lead to: multiple additional pre-operative procedures, more complex and costly MR-guided procedures, and additional surgical procedures to fully excise the target lesion(s). We believe that use of the SCOUT localization procedure might lead to improved excision of the targeted tumor bed, fewer breast procedures, a reduced need for additional operations for margin re-excision and more convenience for the patient, operating room, surgeon, and radiologist scheduling. This will result in lower costs. In addition, the non-wire SCOUT offers surgeons more surgical access options for improved oncoplastic and cosmetic results (1).

2.3.3 Minimization of Risks

IRB approval is required prior to screening and enrollment. Subjects are required to provide signed informed consent prior to participation.

In the event that the SCOUT device is not detected over 31 - 365 days, we have an existing standard of care safety net procedure to use an additional localization device at no charge to the patient (via a second SCOUT device placement and/or standard wire localization).

Patients will be scheduled for their standard of care preoperative imaging 0 – 30 days prior to the scheduled surgery for the radiologists to perform skin marking (standard of care). At that visit, the radiologists will use the SCOUT system to verify that the SCOUT device(s) is detectable from the skin. If the radiologist cannot detect the device(s) at the target, this will be immediately communicated to the surgeon who will determine whether to request an additional SCOUT device(s) or standard wire localization *at no additional cost* to the patient. Although the patient will end up with the standard of care procedure, a slight increased procedure time might occur since the first SCOUT device(s) will need to be removed in addition to the subsequent localization device. We anticipate this risk to be less than 1% (1/150 patients), which is less than routine standard of care (2 - 3%) pre-operative wire localization migration. Vasovagal risks that occur with standard of care pre-operative wire localizations (2 - 3%) have not occurred in our 150 patient experience with SAVI SCOUT. Subjects will be instructed to contact the study investigators about device-related issues. These issues will be promptly communicated to the study investigators for reporting as needed.

2.3.4 Justification for Conducting the Study

Risks to the subjects associated with this study are low. SAVI SCOUT is used routinely by the surgeons participating in this study in this population. The vast majority of these subjects would receive one or more SAVI SCOUT device(s) prior to surgery. The overall increase in risks to the subjects is small and they may benefit from the improved accuracy of identifying the target lesion(s) for surgical excision. This benefit is anticipated to exceed the rare potential instances of device migration or inability to locate the device(s).

In order to protect the privacy of study participants, all study data will be restricted to password protected computers and servers on the protected MHS and Envision Physician Services (formerly Sheridan) networks. Any study data will be de-identified before being sent to a third party.

3. HYPOTHESIS: Placement of the SCOUT device(s) prior to neoadjuvant treatment with biologic (hormonal) and/or chemotherapy allows for long-term localization of breast/axillary lesions targeted for surgical excision.

4. STUDY OBJECTIVES:

Main Objective: To show that the SCOUT device(s) can be used over an extended time (up to 365 days) prior to surgery to successfully guide surgical excision of breast or axillary lesions in patients who undergo neoadjuvant therapy. Preliminary performance and safety information will be collected.

4.1 Study Outcome Measures

4.1.1 Primary Endpoint:

The primary endpoint of this study is successful surgery. Successful surgery (defined as one where the device(s) stays in place and can be removed successfully during surgery) when this device(s) is placed 31 - 365 days prior to surgery. Unsuccessful surgery is defined as one where the device(s) does not stay in place and/or cannot be removed successfully during surgery) when this device is placed 31 - 365 days prior to surgery.

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4.1.2 Secondary Endpoints:

- Number of days prior to surgery (31 - 365) that the SCOUT device(s) is placed by the radiologist to localize the target breast / axillary tissue.
- Success rate of device(s) placement by radiologist (within 1 cm of the center of the target tissue).
- Success rate of SCOUT localization procedure(s) stability. The SCOUT should not migrate more than 5 mm between day 0 - 365 days pre-surgery. This is measured on routine mammogram and/or ultrasound.
- Rate of device(s) related complications.

5. STUDY ENROLLMENT AND WITHDRAWAL:

5.1 Study Population

The study population consists of 25 - 35 adult surgical patient volunteers who plan to have definitive breast cancer surgery at MHS Hospitals after neoadjuvant treatment. Some patient volunteers (estimated 20%) may require more than one and up to four (1 – 4) SCOUT placement (example Breast and Axilla) as is standard of care. Sometimes, additional studies ordered by Medical-Oncology and can impact surgical plan (based on most current National Comprehensive Cancer Network guidelines and/or as a results of multidisciplinary consensus conference).

5.2 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Patient is willing and able to provide informed consent. Patient SCOUT device(s) is placed as part of routine care or study at any time but before neoadjuvant treatment begins.
- Patient is female.
- Patient is between the ages of 18 and 90 years.
- Patient has breast cancer and will undergo neoadjuvant therapy and excision at Memorial Healthcare System.
- Patient is willing and able to comply with all study procedures and be available to follow-up for the duration of the study (1 - 13 months).
- Patient reads or understands English or Spanish.

5.3 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Patient is pregnant.
- Patient has pacemaker or implantable defibrillators (These have not been bench tested as of September 2016).
- Patient has known or suspected nickel allergy.
- Patient is scheduled or receiving *investigational* drugs for neoadjuvant regimen. (This could confound UADE of this device.)
- Patient has any condition that would place the individual at increased risk or preclude the individual's full compliance with or completion of the study.
- Patient has other malignancy except for adequately treated and cured basal or squamous cancer, curatively treated in situ disease or any other cancer for which the patient has been disease free for greater than or equal to 5 years.

5.4 Strategies for Recruitment and Retention

Screening/Enrollment: the investigator will identify subjects from his/her current patient referrals, MHS Breast Tumor Board, and Routine Clinical Preview of Scheduled MHS Breast Patients who may meet inclusion/exclusion criteria. The investigator will determine the interest of the subject to take part in the study. If the subject agrees, the investigator or research nurse will approach the patient to obtain informed consent. Inclusion/exclusion criteria will be verified by the research nurse prior to scheduling the subject for the SAVI SCOUT procedure.

5.5 Treatment Assignment Procedures

In this pilot study, all patients will receive the same treatment assignment, i.e. lesion(s) localization with the SCOUT device(s) 31 - 365 days prior to surgery. Neoadjuvant treatment decisions will be determined by patient's medical oncologist.

5.6 Subject Withdrawal

5.6.1 Withdrawal Procedures

Subjects are free to withdraw from participation in the study at any time upon request. An investigator may terminate a study subject's participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- The subject may elect to withdraw for any reason. However, the subject must either allow for needle-guided (non-surgical) removal by the radiologist or sign a release of records that allows the PI to validate surgical excision at an outside facility.

5.7 Premature Termination or Suspension of Study

Unanticipated Adverse Device Effects (UADE): The sponsor must immediately conduct an evaluation of any unanticipated adverse device effect. A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects must terminate all investigations or parts of the investigations presenting that risk as soon as possible. Termination must occur no later than 5 working days after the sponsor makes this determination and no later than 15 working days after the sponsor was first notified of any UADE or other medical condition in which continued participation in the study would not be in the best interest of the subject.

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the PI and Study Coordinator. If the study is prematurely terminated or suspended, the principal investigator will promptly

inform the IRB and will provide the reason(s) for termination or suspension. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data are not sufficiently complete and/or evaluable.
- Determination of futility.

In compliance with 21 CFR 812.46, if an unanticipated adverse device effect is determined by the sponsor as an unreasonable risk to subjects, termination of the study will occur no later than five (5) working days after the sponsor first receive notice of the effect. The study will not resume without IRB approval and FDA approval.

6. INVESTIGATIONAL INTERVENTION:

6.1 Study Product Description

Commercially available FDA cleared SAVI SCOUT Breast Localization and Surgical Guidance System (Cianna Medical, Inc.), including the console, PROBEs and the temporarily implantable devices will be purchased for this study.

6.1.1 Acquisition

Additional replacement SCOUT devices will be supplied by the device manufacturer, Cianna Medical, Inc., to study subjects at no additional charge if a second device placement is required in the 0 - 365 day pre-operative time period.

6.1.2 Product Storage and Stability

The SCOUT devices will be stored per manufacturer specifications. Devices will be labelled consistent with CFR 812.5 “Caution – Investigational Device. Limited by Federal (or United States) law to investigational use.” Device Accountability that there will be none as SCOUT devices has regulatory authorization to market the device or state whether or not you are going to track the device accountability. SCOUT devices that have been excised and would otherwise be discarded by pathology department after 3 - 4 weeks may be shared with the device manufacturer for purposes of scientific review. This will occur after standard of care pathology department protocol time period has elapsed.

6.2 Study Procedural Intervention(s) Description

6.2.1 Placement of SCOUT Device

Investigator will read over the informed consent (English or Spanish) with potential participants and ensure that they understand the study.

All participants will be given a copy of the informed consent document for their own

reference. Possible participants will be given as much time as is necessary to make an informed decision about whether to take part in the study. The informed consent document reminds them to take their time to make their decision and to discuss the decision with their friends, family and health care team. The study physician will allow the patient to ask as many questions as they want about the process before making an informed decision as whether to take part in the study. Family members will also be encouraged to ask questions and remain involved in the subject's medical care.

Neoadjuvant treatment will be determined by experienced medical oncologist. The breast radiologists are experienced with the device placement and verification techniques (standard of care). The study device(s) will be inserted 31 - 365 days prior to surgery with standard of care technique: image-guidance, local anesthetic, and 16-g needle used to percutaneously deploy the SCOUT device at the target lesion(s). Standard of care post-procedure image verification, audio verification, and skin marking will be performed. SCOUT position will be measured relative to the center of the target lesion(s) will be consistently measured on all breast imaging mammogram/ ultrasound images until surgical excision is confirmed. These measurement will determine whether or not migration > 5 mm occurs in days 0 - 365 days prior to surgery.

Up to 30 days prior to surgery, the standard of care device image verification and skin marking will be performed (at no charge to patient). This visit is performed as standard of care visit, usually within 7 days pre-operatively, and is coordinated with patient's other routine appointments in the same building, such as pre-admission testing. If the SCOUT device(s) is not verified in accurate and stable position (within 5 mm of initial placement as measured on mammogram and/or ultrasound imaging), the surgeon will be notified to determine whether a second localization device or wire placement will be needed. If requested, the placement of a second device using Radiology standard of care technique will be arranged at no expense to the patient up to 30 days prior to surgery.

6.2.2 SCOUT Device Localization

The investigator surgeons are experienced with the device and techniques. The sterile PROBE is used during the procedure to provide continuous guidance for the excision of the device and target tissue.

Standard of care specimen radiograph will be reviewed by the radiologist to verify that the device and target lesion have been obtained. These results are communicated to the surgeon in a time-sensitive manner.

7. STUDY SCHEDULE:

7.1 Screening

- Investigator identifies patients at routine initial treatment planning consultation who require neo-adjuvant therapy.
- Investigator and/or research nurse reviews medical history to determine eligibility

based on inclusion/exclusion criteria.

7.2 Enrollment/Baseline (Study Visit 1 - 31-365 days prior to surgery)

- Patient has SAVI SCOUT LOCALIZATION by Radiologist at any time prior to neoadjuvant treatment SAVI SCOUT placed anytime FDA clearance 10/31/17

- Verify inclusion/exclusion criteria.
- Surgeon and/or MCI research nurse/Investigator
  - complete the **Patient Inclusion/Exclusion Eligibility Enrollment Form**.
  - obtain **consent** from subject on **Informed Consent Form:** Before or after SAVI SCOUT LOCALIZATION and PRIOR TO NACT
  - complete **the Documentation of Consenting Process Form**

- **Research Radiologist**
  - Verifies inclusion/exclusion criteria and Assigns Study ID
  - Completes Device(s) Placement Form
  - *Sends Copy of Consent and Study ID sent to OHR for tracking.*

Sometimes, additional studies ordered by Med-Onc can impact surgical plan.

7.3 Device Placement and Post-Implant Verification (Study Visit 2, Day 0-30 days prior to surgery)

**Breast Radiologist completed standard of care pre-operative skin marking*

Research Radiologist

Completes the Device Placement Form **[Device Placement Recheck]**] on standard of care imaging and performs audio verification and repeat skin marking if requested as standard of care by surgeon.

If not verified, the surgeon must be notified to determine whether the patient must be scheduled for a second localization procedure 0 - 365 days prior to surgery.

7.4 Surgical Excision of Device and Lesion (Visit 3, Operative Day 0)

Research Surgeon

Performs Excision (standard of care)

Completes **Device Surgical Excision Form**

7.5 Study Completion and Unanticipated Device Adverse Event(s) Form (Operative Day 0 + 30 days)

Research Radiologist

Completes **Study Completion Form**

Completes **UADE Form** (as necessary).

**Note distinction of Breast Radiologist (standard of care SCOUT) vs. Research Radiologist (who Completes Forms)*

8. ASSESSMENT OF SAFETY:

8.1 Specification of Safety Parameters

8.1.1 Unanticipated Adverse Device Events

In this study the adverse events from underlying diseases and adverse events related to neoadjuvant treatments will not be collected.

Serious (SADE) adverse device effect or UADE involving risk to subjects or others will be reported to the IRB if the events meets all of the following criteria:

- unexpected in terms of nature, severity, or frequency given: a.) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and b.) the characteristics of the subject population being studied.
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.1.2 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

8.1.3 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death.
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred).
- Results in inpatient hospitalization or prolongation of existing hospitalization.
- Results in a persistent or significant disability or incapacity.
- Results in a congenital anomaly or birth defect.
- An important medical event that may not result in death, be life threatening, or require

hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.4 Adverse Device Effects

Adverse Device Effect is any Adverse Event related to the investigational device. This definition includes AEs resulting from deployment, implantation, operation, or any malfunction of the investigational medical device. Adverse Device Effects will be recorded by the investigator in Case Report Forms. They will be carefully monitored during the entire study.

8.1.5 Unanticipated Adverse Device Effect (UADE)

UADE is any serious adverse effect on health or safety or 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 investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Only unanticipated problems related to the deployment, implantation, and/or function of the SAVI SCOUT will be reported to the IRB/Sponsor. Potential unanticipated device effects include:

- Pain at the SAVI insertion site(s)
- Infection at the SAVI insertion site(s)
- Bleeding at the SAVI insertion site(s)
- Nonfunction of the SAVI
- Unexpected tissue reaction response at SAVI insertion site(s)
- Unexpected limitation of diagnostic quality on routine standard of care imaging

UADE must be reported as soon as possible, but no later than 10 working days after the investigator first learns of the event. If a determination has been made that a UADE presents an unreasonable risk to subjects, the investigation will be terminated no more than 5 days after making the determination and no more than 15 days after receiving notice of the event.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) will be reported, but will be documented and reported to the sponsor. These will not be considered adverse events. If it is possible to return the device, the device will be returned to Cianna Medical, Inc. for evaluation.

Serious Adverse Events including serious adverse device effects and UADEs will be captured throughout the study. Underlying diseases are not reported as AEs and anticipated adverse events related to the neoadjuvant treatment will not be captured.

Serious adverse events from chemotherapy and fertility preservation are ANTICIPATED

and well-documented in the consent form for Chemotherapy and the consent form for Fertility Preservation. Since these SAEs are well-known and considered unrelated to SAVI SCOUT device placement in the breast and/or axilla, the following SAEs will not be reported to the IRB:

CHEMOTHERAPY

Anticipated SAEs from chemotherapy or underlying disease are common and include, but are not limited to:

- Dehydration
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Electrolyte imbalance
- Dizziness
- Loss of appetite
- Weight loss
- Palpitations
- Cardiac arrhythmia
- Heart failure
- Blood transfusions
- Fatigue
- Anxiety
- Hair loss
- Hearing loss
- Balance problems
- Loss of eye sight
- Mouth sores
- Unusual taste
- Sore throat
- Lung damage
- Problems breathing
- Burning when passing urine
- Blood in the urine
- Elevated blood sugar
- Kidney damage
- Renal failure
- Loss of fertility
- Pain in jaw
- Weak muscles
- Change in mood (angry, depressed)
- Altered mental status and confusion

- Nerve damage (lose ability to move parts or all of body, tingling in extremities)
- Low white or red blood cell count with increased risk of fatigue
- Infection
- Low platelet count with increased risk of bruising and bleeding
- Cardiac toxicity
- Small risk of development of leukemia and shortness of breath
- Veins at chemotherapy infusion site may harden, become painful, or develop sores and the skin tissue in the surround area may be destroyed.
- The chemotherapy treatment may cause a new cancer to form.

FERTILITY PRESERVATION

Anticipated serious adverse events from fertility preservation/egg harvesting or underlying disease are common and include but are not limited to:

- Adult and childhood cancer
- Infertility
- Infection at the medication injection site
- Pain at the medication injection site
- Infection associated with egg retrieval or embryo transfer
- Pelvic infection
- Abdominal infection
- Damage to other intra-abdominal organs during the egg retrieval
- Damage to the bowel, appendix, bladder, ureters, and ovary
- Genetic problems in children born from Intracytoplasmic Sperm Injection (ICSI)
- Birth defects
- High-order multiple gestations (triplets or greater)
- Damage to the embryo
- Cerebral palsy
- Developmental delay.
- Normal risks of subsequent pregnancy include pregnancy loss, gestational diabetes.

Ovarian Hyperstimulation Syndrome (OHSS) is a serious side effect. Symptoms can include:

- Increased ovarian size
- Nausea
- Vomiting
- Accumulation of fluid in the abdomen which could require drainage
- Breathing difficulties
- Increased concentration of red blood cells
- Kidney problems
- Liver problems
- In the most severe cases, blood clots, kidney failure, or death

Potential side effects include, but are not limited to:

- Hot flashes
- Vaginal dryness
- Bone loss
- Nausea
- Vomiting
- Fluid retention
- Muscle aches
- Headaches
- Change in Mood (Depression/Anxiety)
- Abdominal pain
- Skin reaction at the injection site
- Sleepiness
- Allergic reaction

If given by intra-muscular injection includes the additional risk of:

- Infection at the injection site
- Pain at the injection site
- Irritation at the application site

If given by transdermal route:

- Risk of stroke
- Increased moodiness
- Vaginal infection
- Diarrhea
- Rashes
- Sensitivity to the sun
- Allergic reactions
- Drowsiness
- Severe infections
- Damage to the internal organs.
- Abdominal discomfort could result in the need for hospitalizations for observation purposes
- Cysts could rupture requiring emergency surgery to stop the bleeding and could result in a need for blood transfusions and possible loss of one or both ovaries, the stimulated ovary can twist on itself, cutting off its own blood supply.
- Feelings of anxiety, depression, isolation, and helplessness are not uncommon among patients undergoing chemotherapy and/or infertility treatment.
- Strained and stressful relations with spouses, partners and other loved ones are not uncommon as treatment gets underway and progresses.

8.2 Time Period and Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded in the data collection system throughout the study.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 30 days (for non-serious AEs) or 7 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3 Characteristics of an Adverse Event

8.3.1 Relationship to Study Intervention

To assess relationship of an event to study intervention, the following guidelines are used:

8.3.1.1 Related (Possible, Probable, Definite):

- The event is known to occur with the study intervention.
- There is a temporal relationship between the intervention and event onset.
- The event abates when the intervention is discontinued.
- The event reappears upon a re-challenge with the intervention.

8.3.1.2 Not Related (Unlikely, Not Related):

- There is no temporal relationship between the intervention and event onset.
- An alternate etiology has been established.

8.3.2 Expectedness of SAEs

The PI will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

8.3.3 Severity of Event

The following scale will be used to grade adverse events:

- Mild: no intervention required; no impact on activities of daily living (ADL).
- Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL.
- Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL.

8.4 Reporting Procedures

8.4.1 Unanticipated Problem Reporting to IRB

Incidents or events that meet the criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. The following information will be captured when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB and to the study sponsor to evaluate regarding FDA reporting guidelines:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number.
- A detailed description of the adverse event, incident, experience, or outcome.
- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem.
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB, Monitor and study sponsor within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB, Monitor and study sponsor within 2 weeks of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and study sponsor.

The study will adhere to monitoring consistent with CFR 812.46, which requires:

(i) Securing compliance. A sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, the requirements of this part or other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA shall promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. A sponsor shall also require such an investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

(ii) Unanticipated adverse device effects. A sponsor shall immediately conduct an evaluation of any unanticipated adverse device effect. A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect.

(iii) Resumption of terminated studies. If the device is a significant risk device, a sponsor may not resume a terminated investigation without IRB and FDA approval. If the device is not a significant risk device, a sponsor may not resume a terminated investigation without IRB approval and, if the investigation was terminated under paragraph *(ii)* of this section, FDA approval.

9. STATISTICAL CONSIDERATIONS:

Study Hypothesis: Placement of the SCOUT device prior to neoadjuvant treatment with biologic (hormonal) and/or chemotherapy allows for long-term localization of breast/axillary lesions targeted for surgical excision.

Main Objective: To show that the SCOUT device can be used over an extended time (up to 365 days) prior to surgery to successfully guide surgical excision of breast or axillary lesions in patients who undergo neoadjuvant therapy. Preliminary performance and safety information will be collected.

9.1 Sample Size Considerations

This is a pilot study. It is felt that up to 25 - 35 subjects will provide a reasonable estimate for the efficacy of the method.

9.2 Final Analysis Plan

Simple statistics will be used to evaluate the collected data as to the data elements listed in the primary and secondary endpoints.

10. SOURCE DOCUMENTS AND ACCESS to SOURCE DATA/DOCUMENTS:

MHS and Envision Physician Scientific Research (formerly Sheridan Scientific Intelligence) will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects.

The main source of data will be the electronic and/or physical medical records of our institution. In addition to basic demographic information, notes from the appropriate radiologic, surgical and pathology procedures will be accessed in order to complete the case report forms.

Note that the forms must be completed at the time of the relevant procedure by the study coordinator and/or investigator, since these data might not be captured in the standard reports.

Patient Inclusion/Exclusion Eligibility Enrollment Form
Device Placement Form
Device Excision Form
Unanticipated Adverse Device Event(s) Form(s)
Study Completion Form

De-identified (identified by study ID number only) copies of all medical images depicting the breast lesion and SCOUT device may be shared for scientific presentations. These images are necessary for complete analysis of the reasons if there is any possible failure of the detection of FDA cleared SCOUT system over a longer duration prior to breast and/or axillary lymph node surgery. These images include the following:

1. Diagnostic imaging
2. Image-guided device placement
3. Imaging of device verification (if available)
4. Additional localization imaging (if necessary)
5. Post-excision specimen radiograph

All DICOM images should be de-identified according to the guidelines specified by the NCI Cancer Imaging Archive. For details, see:

https://wiki.cancerimagingarchive.net/display/Public/De-identification+Knowledge+Base

11. ETHICS AND PROTECTION OF HUMAN SUBJECTS:

11.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

11.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the local IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

11.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. Patients may have SAVI SCOUT LOCALIZATION by the Radiologist at any time prior to NACT as SAVI SCOUTs may be placed anytime per FDA clearance 10/31/17 (2). The subject will sign the informed consent document prior to any study-related activities. Subjects

will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing that the quality of their clinical care will not be adversely affected if they decline to participate or withdraw from this study. The consent process will be documented in the clinical or research record.

11.3.1 Waiver of Authorization

A Waiver of HIPAA Authorization for PHI access will be requested, as in addition to identifying potential subjects from current patient referrals, investigators will also identify potential subjects from the MHS Breast Tumor Board and MHS Routine Clinical Preview of Scheduled Breast Patients. There is no more than minimal risk to privacy of individuals due to an adequate plan to protect identifiers from improper use and disclosure, an adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research, PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research which the use of disclosure of PHI would be permitted, and the research could not practicably be carried out without the waiver or without access to and use of PHI.

11.4 Exclusion of Women, Minorities, and Children (Special Populations)

There will be no exclusion based on race and ethnicity. No vulnerable patient populations are included in this study. Minors have been excluded because their breast tissue may be atypical for the target population. Although breast cancer in males is rare, these patients have also been excluded from this study since very few if any require pre-operative localization of any type for diagnosis or treatment purposes. Pregnant women are also excluded from participating as it remains unknown at this time how long-term presence of SAVI SCOUT in a pregnant female impacts unborn child.

11.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the IRB may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic or hospital) for the study subjects. The clinical study site will permit access to such records.

This study will collect and utilize certain data elements that could be used to identify the participants. However, the study will not use any information that, if released, could reasonably place participants at risk of criminal or civil law suits.

To maintain the privacy and confidentiality of the research subject's data, all paper documents containing PHI will be stored in locked file cabinet(s) in a locked room. For electronic data, all documents will be stored on password-protected computers and/or secured servers that are backed up nightly. All study data will be maintained in password-protected files, for which only authorized study team members have the password.

Any study data that is sent to outside third parties for data analysis will be completely de-identified.

Master files containing study-related data will be stored for 3 years as requested by FDA Title 21 CFR 58.195.

11.6 Future Use of Stored Specimens and Other Identifiable Data

No specimens or other identifiable data will be retained in this study for future use.

12. DATA HANDLING AND RECORD KEEPING:

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

12.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff to ensure that they are accurate and complete. The investigator or designee must review unanticipated problems and adverse events.

Completed Case Report forms will be kept in a locked file cabinet and only study personnel will have access to them.

12.2 Study Records Retention

No records or devices will be destroyed without the written consent of the principal investigator. Records will be maintained for 3 years as recommended by FDA Title 21 CFR 58.195.

12.3 Protocol Deviations

Protocol deviations will be handled in accordance with IDE non-significant risk standards of FDA Title 21 CFR 812, which specifies the following:

There are occasions when a failure to comply with the protocol may be considered a failure to protect the rights, safety, and welfare of subjects because the non-compliance exposes subjects to unreasonable risks. For example, failure to adhere to inclusion/exclusion criteria that are specifically intended to exclude subjects for whom the study drug or device poses unreasonable risks may be considered failure to protect the rights, safety, and welfare of the enrolled subject. Similarly, failure to perform safety assessments intended to detect drug toxicity or device safety within protocol-specified time frames may be considered failure to protect the rights, safety, and welfare of the enrolled subject. Investigators will seek to minimize such risks by adhering closely to the study protocol.

13. COSTS:

13.1 Costs to Subject

This study will incur no costs to the subjects other than those considered standard of care. All research-related costs will be budgeted and covered by Memorial Healthcare System, Sheridan Radiology Services and by the study sponsor Cianna Medical, Inc.

13.2 Payment for Participation

Subjects will not be paid for their participation.

14. REFERENCES:

1. Cox CE, Garcia-Henriquez N, Glancy MJ, Whitworth P, Cox JM, Themar-Geck M, Prati R, Jung M, Russell S, Appleton K, King J, Shivers SC. Pilot study of a new nonradioactive surgical guidance technology for locating nonpalpable breast lesions. *Ann Surg Oncol* 2016; 23 (6): 1824 - 1830.

2. Food & Drug Administration [FDA]. RE: K171767 Trade/device name: Cianna Medical SAVI Scout reflector and SAVI Scout system. U.S. Food & Drug Administration. https://www.accessdata.fda.gov/cdrh_docs/pdf17/K171767.pdf. Published October 2017. Updated November 6, 2017. Accessed March 12, 2018.

3. Caudle AS, Yang WT, Mittendorf EA, Black DM, Hwang R, Hobbs B, Hunt KK, Krishnamurthy S, Kuerer HM. Feasibility trial for selective surgical localization of axillary lymph nodes containing metastases in breast cancer patients. *JAMA Surg*. 2015; 150 (2): 137 - 143.

4. Hylton NM, Gatsonis CA, Rosen MA, Lehman CD, Newitt DC, Partridge SC, Bernreuter WK, Pisano ED, Morris EA, Weatherall PT, Polin SM, Newstead GM, Marques HS, Esserman LJ, Schnall MD. Neoadjuvant chemotherapy for breast cancer: functional tumor volume by MR imaging predicts recurrence-free survival - results from the ACRIN 6657/CALGB 150007 I-SPY 1 TRIAL1. *Radiology* 2016; 279 (1): 44 - 55.

5. Mango V, Ha R, Gomberawalla A, Wynn R, Feldman S. Evaluation of the SAVI SCOUT surgical guidance system for localization and excision of nonpalpable breast lesions: a feasibility study. *AJR Am J Roentgenol.* 2016; 15: W1 - W4.

15. PARTICIPATING INSTITUTIONS:

Institution City, State	Enrollment Started	Principal Investigator Phone E-mail
Memorial Healthcare System Envision Physician Scientific Research Radiology Associates of Hollywood, Inc.	2016	Mary K. Hayes, M.D. 954. 265. 6311 mhayes@mhs.net

16. SUPPLEMENTAL MATERIALS:

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

1. SAVI SCOUT Operating Manual
2. SCOUT Non-Significant Risk (NSR) Justification
3. IFU Reflector SAVI SCOUT
4. Case Report Forms
5. Cianna Medical, Inc. SAVI SCOUT FDA Clearance for Long-Term Use Letter
6. Study Personnel “Cheat Sheet” for Enrollment