NCT04066699

Percutaneous Localization: Open-label Registry of Thoracic Surgery (PLOTS)

IRB Approved Protocol – 2 November 2020

THE PLOTS REGISTRY STUDY PROTOCOL

TITLE	Intraoperative, Percutaneous Localization of Peripheral Pulmonary Nodules for Resection: a Prospective, Open-Label, Multi-Center Registry Study of Thoracic Surgery Outcomes.
PROTOCOL/STUDY NO.	VMT-01-003
WESTERN IRB TRACKING NO.	20191713
VERSION	Current: 02November2020 Prior: 11June2019 Amendment #: 1
SPONSOR	Veran Medical Technologies, Inc. 1938 Innerbelt Business Center Drive St. Louis, MO 63114 USA
CONDUCTED BY	Veran Medical Technologies, Inc. 1938 Innerbelt Business Center Drive St. Louis, MO 63114 USA

Confidentiality Statement

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Principal Investigator's Signature Page

Short Study Title: PLOTS Registry

Intraoperative, Percutaneous Localization of Peripheral Pulmonary Nodules for Resection: a Prospective, Open-Label, Multi-Center Registry Study of Thoracic Surgery Outcomes.

I have read and understand the protocol and agree that it contains the ethical, legal, and scientific information necessary to participate in this study. My signature confirms that the study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to the Requirements of 21 CFR 50 and 56; 21 CFR 11; 21 CFR 803; 21 CFR 812.2(c); 45 CFR 46 , as they relate to medical device registries of marketed commercial devices used within their labeled indication and instructions for use.

I will provide copies of this protocol as needed to all physicians, nurses, and other professional personnel responsible to me who will participate in the Study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the conduct of the Study. I am aware that this protocol will need to be approved by an appropriate Institutional Review Board (IRB) prior to any subjects being enrolled and that I am responsible for verifying whether that requirement is met. I agree to adhere to the attached protocol and if requested to provide copies of medical information for the purpose of verification of submitted information.

Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

Investigator:

_____
Print Name

_____ _____
Signature Date

_____
Print Name of Institution or Practice and Location

RETURN ORIGINAL TO Veran Medical Technologies
RETAIN COPY FOR INVESTIGATOR FILE

Veran Medical Technologies Signature Page

Reviewed and Approved by:

Name	Signature	Title	Date
Name	**Signature**	**Title**	**Date**

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LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
AE	Adverse event
ASCO	American Society of Clinical Oncology
BMI	Body Mass Index
CFR	Code of Federal Regulations
CT	Computed Tomography
CTCAE	Common terminology for adverse events
DL_{CO}	Diffusing capacity of the lungs for carbon monoxide
EBUS	Endobronchial ultrasound
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
EMN	Electromagnetic navigation
FB	Flexible bronchoscopy
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed consent form
ICH	International Conference on Harmonization
ACMJE	American Committee of Medical Journal Editors
IFU	Instructions for Use
IRB	Institutional review board
IR	Interventional Radiologist/Radiology
Kg	Kilogram
LDCT	low-dose computed tomography
mcg	Microgram (μg)
mg	Milligram
mL	Milliliter
MedDRA	Medical Dictionary for Regulatory Activities
MIV	Minimally invasive
mm	Millimeter
NCCN	National Comprehensive Cancer Network
PI	Principal Investigator
PPN	Peripheral pulmonary nodules
SAE	Serious adverse event
SD	Standard Deviation
SOP	Standard Operating Procedures
SPiN or SPiN System	SPiN Thoracic Navigation System™
US	United States of America
VATS	Video assisted thoracoscopic surgery
VERAN	Veran Medical Technologies, Inc.

STUDY SYNOPSIS

SPONSOR	Veran Medical Technologies, Inc.
PRODUCT	SPiN Thoracic Navigation System™, including Localization Needles, SPiN Perc™ Kit, other accessories per investigator discretion
TITLE	Intraoperative, Percutaneous Localization of Peripheral Pulmonary Nodules for Resection: a Prospective, Open-Label, Multi-Center Registry Study of Thoracic Surgery Outcomes.
STUDY NUMBER	VMT-01-003
STUDY PHASE	Post-marketing Registry/IV
LOCATION	This trial will be conducted at approximately 5 sites across the US.
NUMBER OF SUBJECTS	The study aims to report 70-100 subjects. Each site is expected to enroll a minimum of 6 subjects.
OBJECTIVES	The registry is aimed developing a high-quality set of data regarding intraoperative percutaneous localization of peripheral pulmonary nodules (PPNs), and then identifying and promulgating efficient, evidence-based best practices for this technique. The resection procedure itself is standard of care and follows the investigator's standard protocol. Successful localization of PPNs is a challenge involving multiple factors, beginning with the subjects' health, lung function and also factors specific to the nodule including location within the lung, size, distance from the lung surface, whether solid or ground glass and proximity to a fissure. Hard to see or palpate nodules are currently localized with dye and/or hook wires or fiducials, either endoscopically or percutaneously. Successful, large, prospective studies have not been reported using modern electro-magnetic navigation (EMN)-guided percutaneous intraoperative localization, and different techniques (dye vs. fiducial vs. hook wire etc.) have not been evaluated. It is for these reasons that the different localization techniques used with EMN-guided percutaneous localization will be collected for patients having a suspicious nodule and who undergo percutaneous intra-operative localization and immediate resection. This registry aims to record the localization techniques used by thoracic surgeons and IP/surgical teams to identify PPNs using the SPiN Thoracic Navigation System™ in the hands of trained physicians. The objectives of this study will be to accomplish the

	primary and secondary objectives listed below, and to observe localization in a real-world context of pulmonary resection.
PRIMARY OBJECTIVE	**Successful percutaneous localization of PPN.** This is defined as the percentage of subjects in whom the nodule is successfully localized and removed in the first resected specimen. A pathological specimen with clear margins will count as a successful localization.
SAFETY OBJECTIVES	1. Report the incidence of device-related adverse events that occur during the localization procedure.
SECONDARY OBJECTIVES	1. Report localization methods and techniques – dye and materials used, volume of dye (methylene blue, ICG etc.), other materials such as microcoils, hook wires etc. Details regarding these techniques will be collected. 2. Collect data on intraoperative percutaneous localization time and duration of total surgical procedure. 3. Record nodule characteristics, including location in the lobe, distance from pleura, distance from surface of skin to target, morphological appearance, solid vs ground glass etc. 4. Record weight of excised tissue and margin. 5. Report type of surgical resection performed (segmentectomy or wedge) and resection technique (VATS, RATS, thoracotomy).
STUDY DESIGN	The registry is designed to collect data about subjects who fall within the current practice, and to better understand effective intraoperative localization techniques used by thoracic surgeons to localize small, suspicious lesions just prior to surgery. The SPiN System and tools are a medical device that is 510(k) exempt under 21 CFR 812.2(c)(2), which applies to the investigation. The 510(k) product is being used in accordance with the product labeling (Appendix A). This is a prospective, multicenter, open-label, single arm registry to record the safety, efficacy, and methodology of percutaneous, intraoperative localization of PPNs immediately prior to lung resection. As such, it is a technical procedure registry designed to better understand the various factors which affect percutaneous localization. Thoracic surgeons of varying levels of experience in EMN-guided percutaneous localization will be trained on localization tools and techniques using the SPiN System – with didactic peer-to-peer presentations, followed by device training and hands-on experience with phantoms and/or cadavers.

	The study will enroll between 70 and 100 subjects who fall within current clinical practices to have their PPNs removed at approximately 5 geographically diverse sites across the US. These subjects will undergo intraoperative, EMN-aided percutaneous nodule localization and subsequent resection as part of their normal care. Safety data (adverse and severe adverse events) regarding these subjects will be collected for the localization procedure. All surgical and post-surgical treatment decisions and clinical assessments will be at the discretion of the subject's thoracic surgeon. Eligible subjects from participating sites will be enrolled following identification of a qualifying nodule, and meeting inclusion/exclusion criteria and completing informed consent. *Data Collection* Registry data will be collected before, during, and after the procedure from the subject's medical records by site personnel. Based on current clinical practice, it is anticipated that subjects will be seen following nodule identification and workup to determine the treatment plan and preparation for surgery (baseline visit). The size and location of the nodule, demographic data and data about smoking history will be collected. Comorbidities will be collected from medical history, and the subject's lung function test results collected. The subject will return to the site for surgery. A non-contrast chest CT scan is recommended within 24 hours/same day as surgery, as a clinically indicated procedural planning tool (Appendix D – Veran CT scan). Otherwise, a non-contrast chest CT scan within the past 15 days is adequate. Subjects are typically given general anesthesia for surgery. The localization technique and material used will be recorded, including volume and type of dye, which needle used, and any other fiducial markers (e.g. microcoil). Localization procedure-related adverse events and device-related adverse events will be recorded. The type and technique of resection performed will be collected (VATS, RATS, thoracotomy, etc.). Subjects recover in hospital and are discharged per standard of care. Any localization-related adverse events will be reported, however the overall lung surgery procedure itself is not being studied (approved indication). Subjects will typically return to the clinic a few times to be seen for scheduled post-operative visits to monitor recovery. A secure, site portal that is 21 CFR part 11 compliant is used for the electronic data entry and reporting at each site, which includes appropriate firewalls between sites and users to protect subject

	PHI and privacy. All data collected into the study database will be de-identified at the site level.
STUDY PROCEDURES	Subjects are treated for lung resection according to the treatment devised by their clinician. Part of the technical procedure registry trains thoracic surgeons on the various available tools and techniques in intraoperative localization, using both didactic review, best practices, case review, and a cadaver lab. The following represents the typical standard of care for this procedure. The registry study is nested within the standard lung resection operation, and study procedures on data collection are described within the context of these procedures for clarity of identification: Following nodule identification and referral, subjects are typically evaluated per the subject inclusion/exclusion criteria. Review of the subject's CT/PET scan demonstrate a PPN that is between 0.4 cm and 3.2 cm in its longest dimension. All subjects will sign and date an Informed Consent Form (ICF) before enrollment (Baseline Visit). Subjects will undergo a chest CT scan on the day of surgery, verifying the longest dimension of the nodule (data collected). The subject is put under general anesthesia. The SPiN Percutaneous nodule localization procedure is performed intraoperatively, using dye and/or other localization techniques. A surgical resection (wedge, segmentectomy etc.) will follow, according to PI's judgment. Subjects are generally hospitalized between 2-5 days following this procedure and discharged. Following discharge, subjects typically follow a schedule of multiple clinic visits, as determined by their healthcare team. Subject participation in the localization registry will end following hospital discharge.
ESTIMATED DURATION OF STUDY	The Registry is anticipated to take 24 months to complete.

STUDY POPULATION	The target subject population includes adult subjects (18 years-85 years), with PPNs. In the judgment of the thoracic surgeon, localization for resection is warranted via a percutaneous localization approach. The establishment of malignancy is not necessary for PPN removal. Data will be collected from study subjects having a PPN between 0.4 cm and 3.2 cm in greatest dimension, that are accessible to percutaneous localization, who consent to and undergo intraoperative dye/wire localization procedure followed by surgical lung resection.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Subjects will be eligible to enroll into the registry if they have given their informed consent and also meet the following criteria: **Inclusion criteria:** • Subject's physician and/or thoracic surgeon have deemed/has deemed that the surgical removal of the PPN is appropriate. • A clinical decision has been made to use the SPiN Thoracic Navigation System™. • Subject is at least 18 years of age at time of study entry. • Subject is able to read, understand, and voluntarily sign the IRB-approved informed consent document prior to the performance of any study-specific procedures. IRB-approved translation may be used if indicated. Reasonable accommodation of visually impaired subjects will be allowed. • Subject is able to tolerate general anesthesia. • Subject has a target nodule between 0.4 cm and 3.2 cm in greatest dimension; • The target nodule is in a location that is accessible for percutaneous localization in the judgement of the surgeon. **Exclusion criteria:** • Subjects with any other concomitant treatment or medical condition that, in the opinion of the clinician, would render peripheral nodule resection more hazardous than beneficial. • Subject is pregnant. • Pulmonary nodule is greater than 3.2 cm. • Subjects with significant coagulopathy having INR >2.0 or PTT> 2x normal. • Subject is unable to tolerate general anesthesia • Obese subject, impacting percutaneous access (BMI >50)
TEST PRODUCT AND MODE OF ADMINISTRATION	Localization of nodules will be completed with the SPiN Thoracic Navigation System™, and the corresponding tools that allow for percutaneous access. These include the SPiN Perc™ Kit and the 1 cm and 2 cm Localization Needles. Please refer to protocol section 5, and also the IFU and product information (Appendix A). Investigators are trained in the use of the tools and the system.

REFERENCE THERAPY	Historical data as available.
DURATION OF SUBJECT INVOLVEMENT	Duration of treatment studied during the registry will be up to approximately 6 weeks per subject, including screening and baseline visits, surgery, and hospital visit.
SAFETY ASSESSMENTS	Localization-related events will be collected.
STATISTICAL ANALYSIS	*Statistical Considerations* This is a registry study where no formal hypothesis is being tested. Data collected during the study will be summarized using descriptive statistics and graphical displays. Generally, demographic and other descriptive characteristics will be described as counts and percentages for categorical variables and as measures of central tendency (mean, median, standard deviation [SD], and range) for continuous variables. Ninety five percent (95%) confidence intervals will be presented for key variables and measures of effect. In some cases, data may be summarized by demographic, response, or treatment subgroups (for example by age, sex, nodule size, smoking history and post-surgical smoking pack years, pulmonary function tests, etc.). No adjustments will be made for multiple comparisons. All localization-related adverse events will be listed and summarized. *Interim and Final Analyses* Data collected during the study, which is open-label and non-randomized, will be analyzed and reported periodically by an executive steering committee comprised of thoracic surgeons. When the study is completed, a final analysis will be performed and reported.
DATE OF ORIGINAL PROTOCOL	June 11, 2019
DATE OF AMENDMENT	November 2, 2020

1. STATEMENT OF COMPLIANCE

This human subject study will comply with all applicable federal, state, and local laws and regulations, including generally accepted standards of good clinical practice as adopted by current Food and Drug Administration ("FDA") regulations and statutes. Participating study sites shall only allow individuals who are appropriately trained and qualified to assist in the conduct of the Study.

2. BACKGROUND

Within the past several years, small and suspicious pulmonary nodules have raised a difficult issue for internal medicine physicians, pulmonologists, interventional radiologists, and cardiothoracic surgeons. Depending upon the size, location, and type of nodule, they can be challenging to precisely locate and remove. The nodules, including those studied here between 0.4 cm and 3.2 cm along their longest axis, are often found incidentally usually on Computed Tomography (CT) scans and sometimes on chest X-rays. In studies of incidentally detected nodules, the prevalence of malignancy ranges from 2-82% (Wahidi *et al*, 2007).

There is an opportunity to develop efficient tools and procedures to more precisely target these PPNs. Depending on the patient, this targeted approach may also offer the best opportunity to preserve as much remaining lung function as possible in cases where subjects have respiratory comorbidities. Thus, developing and describing a streamlined, reproducible and accurate approach to nodule localization is a method that holds promise for thoracic surgeons.

Current recommendations from the American College of Chest Physicians (ACCP) evidence-based guidelines for the management of pulmonary nodules begin with examination of the nodule, and an estimation of the clinical probability that the nodule is malignant and evaluation of surgical risk. For subjects with a high probability of cancer (>60%), diagnosis by biopsy and resection are recommended. More than 40% of lung targets are not accessible by conventional bronchoscopy due to their location, with contributing factors including the small diameter of the airways, lack of an airway leading to a nodule and maneuverability difficulties (Rivera et al, 2003; Alberts and Colice, 2003).

The ability to identify and to obtain diagnostic tissue from PPNs has been evaluated in clinical trials using techniques such as diagnostic bronchoscopy alone, and then in comparison, with EMN-guided bronchoscopy and r-EBUS (Ost *et al.,* 2016). A large, multicenter registry-based clinical effectiveness study (AQuIRE Registry) (*ibid..).* The AQuIRE registry had a primary objective to measure and identify the determinants of diagnostic yield for bronchoscopy in patients with peripheral lung lesions. Secondary outcomes included diagnostic yield of different sampling techniques, complications, and practice pattern variations. Subjects were enrolled at 15 centers having 22 study physicians between 2009-2014, and the registry was funded by the CHEST organization.

Ost *et al.* reported unexpectedly low diagnostic yields for electromagnetic navigation. Regarding the low EMN rate, one AQuIRE principal investigator (PI) noted "more than 98% of the EMN cases were performed with a single system (Medtronic, Minneapolis, MN) that lacks additional capabilities, including TTNA under EMN guidance. Since the completion of enrollment in the AQuIRE study, newer EMN technologies have been developed and now allow for a navigational transthoracic approach."

- The AQuIRE registry had a primary objective to measure and identify the determinants of diagnostic yield for bronchoscopy in patients with peripheral lung lesions. Secondary outcomes included diagnostic yield of different sampling techniques, complications, and practice pattern variations.
- The AQuIRE registry reported poor diagnostic yields for multiple modalities
    - Bronchoscopic alone: 53.7%
    - r-EBUS when used alone: 57%
    - EMN Yield when used alone was 38.5% (98% of cases were SuperDimension technology)

Of these, 312 subjects in the trial underwent transbronchial biopsy. Using bronchoscopy alone, the diagnostic yield was reported as 63.7%. In earlier work, the average diagnostic yield for peripheral lung lesion biopsy performed with conventional flexible bronchoscopy was reported to be 69% for peripheral lesions greater than 20 mm and 33% for peripheral lesions less than 20 mm, (Mazzone et al, 2002; Rivera et al, 2003; Schriebner and McCrory, 2003).

Results from studies involving procedural guidance technologies such as electromagnetic navigation (EMN) and radial endobronchial ultrasound (radial EBUS) have also been reported (Ost *et al*., 2016). Diagnostic yield was reported at 57% with r-EBUS alone, 47.1% with EMN combined with r-EBUS. In another recent study published in the New England Journal of Medicine, a total of 639 subjects underwent bronchoscopy for suspected lung cancer and of those bronchoscopic examinations, 43% were nondiagnostic, including in 25% (120 of 487 subjects) in whom lung cancer was ultimately diagnosed.[9] As a result of published yields showing an unacceptable yield for peripheral bronchoscopy, ACCP guidelines recommends that nodules without a CT-bronchus sign should be pursued with EMB-TTNA (Rivera et al, 2013).

Veran's novel electromagnetic system (EMN) bronchoscope and toolkit use the EMN field with several "Tip Tracked" nodule localization instruments, and a bronchoscope to generate three dimensional maps of lung tissue and airways. The "Tip Tracked" instruments display their location during the procedures. The generated maps provide continuous, "real-time" navigational tracking, identifying an efficient path to localizing nodules only a few millimeters along their longest axis. Providing the operator with assisted lung nodule localization and navigation have improved diagnostic yields. The system uses the recent chest CT scan image and combines it with the bronchoscope to align the subject's body with the CT images. This allows for the construction of 3-D virtual bronchoscopy images and the ability to navigate throughout the lung with a CT-correlated roadmap. As the operator steers the bronchoscope, a real time distance to target is generated, that can be used for the precise localization of small lesions.

Localization of the peripheral nodules in the outer lung regions can be accomplished intraoperatively, just prior to surgical resection, with the same surgical staff who are performing the operation. This eliminates an additional step for the thoracic surgeon (or other oncology team member) and also for the subject, namely identifying and coordinating with persons from other departments who may typically place fiducial, hookwire, and microcoils as separate procedures, involving additional resources. In addition, the migration of these markers, and the need to verify their placement with an additional CT or other scan prior to surgery, are potentially steps that may be able to be streamlined. The overarching objective is to keep this localization and resection procedure within the hands of the principal investigator, and to quantify the percentage of subjects in whom the nodule is removed in the first resected specimen, procedure time, and nodule characteristics and procedure details and techniques.

3. RATIONALE

Veran Medical Technologies, Inc. is seeking to characterize the efficient localization and successful removal of PPNs aided by the technique of percutaneous localization within the operating room. This falls within the current practice for these subjects. However, the characterization and comparison of various localization techniques has not been reported prospectively in a large, multicenter approach.

To realize this opportunity, further localization methodologies must be developed. Percutaneous nodule localization involves various factors. Nodular size and location (near the pleura) can both introduce challenges for unequivocal localization and complete removal. PPNs can be difficult to locate and access in order to mark them. It can be difficult to find the marked nodules, depending upon the location and how well the localization technique worked during the resection surgery. This registry will collect data regarding different techniques used by thoracic surgeons using a choice of localization materials (dye, hookwire etc.) and with electromagnetic navigation guidance using a transthoracic approach. Evidence from a multicenter, prospective registry trial on localization procedures will allow us to understand the best practices in the localization of PPNs that also minimizes risks in subjects who are typically are older, have comorbid lung disease, poor pre-surgical lung function and may have early stage lung cancer.

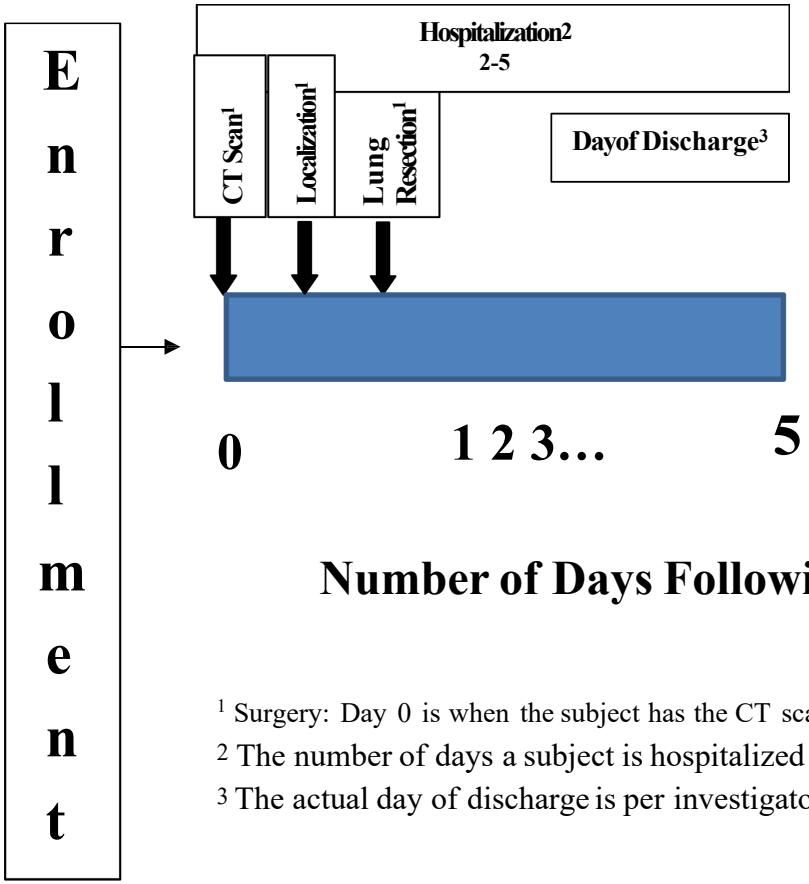
Further, the study will allow us to describe the use of VERAN SPiN Thoracic Navigation System™ and percutaneous lung localization tools in a real-world thoracic surgery practice, including duration of localization procedure, duration of the resection procedure, and other data elements.

TABLE 1 – SCHEDULE OF EVENTS

Procedures/Data Collection	Baseline Visit	Day 0 Surgery Localization Procedure
Nodule is correct size and suitable for percutaneous localization during surgical resection procedure.	X	X
Subject meets Inclusion/Exclusion criteria review.	X	
Subject is able and willing, and signs consent form.	X	
Pregnancy test- urine or serum, for females of child-bearing potential.	X	X
Socio-demographic information.	X	
Pulmonary function test results	X	
Brief Medical History, including previous cancer diagnoses, smoking, and treatment history.	X	
Nodule hx, dx, characteristics if known.	X	
Recent (0-15 days) CT scan available, or schedule CT scan to be used on day of surgery, prior to procedure.	X	X
AEs and SAEs.	X	X
Reason for discontinuation in study or withdrawal if applicable.		

All data generated from this study will be the exclusive property of Veran Medical Technologies, to be used with expressed permission only.

TABLE 2 – Registry Study Flow[1]



[1] Surgery: Day 0 is when the subject has the CT scan, procedure of PPN Localization and also lung resection.

[2] The number of days a subject is hospitalized is per investigator practice. It is recorded as a data element.

[3] The actual day of discharge is per investigator's practice. It is recorded as a data element.

4. OBJECTIVES

The registry is aimed at developing a high-quality set of data regarding the percutaneous localization of PPNs. The localization registry itself is nested within the subjects' lung resection operation. Analyzing and promulgating evidence-based best practices for lung nodule localization will allow surgeons to identify technical solutions and reproducible methods.

This registry will record procedural data for trained thoracic surgeons using the SPiN Thoracic Navigation System™ and tools. Diagnostic yield will measure successful localization of the lesion in the resected specimen. Localization-related safety events will be collected.

4.1 Primary Objective:

Successful percutaneous localization of PPN.

To evaluate the accuracy of percutaneous nodule localization using the SPiN Thoracic Navigation System™ and its accessories, Veran will record the percentage of successful resections that result in the complete removal of the patient's nodule, with a negative margin. The diagnostic yield is calculated as the percentage of patients who have intra-operative localizations resulting in complete removal of nodule, divided by the total number of evaluable subjects. Evaluable subjects are those who complete the localization procedure.

Primary Objective: Successful percutaneous localization of PPN.
This is defined as the percentage of subjects in whom the nodule is successfully localized and removed in the first resected specimen. A pathological specimen with clear margins will count as a successful localization.

4.2 Safety Objective:

Collect safety data for localization procedure.

4.3 Secondary Objectives:

Secondary Objectives: Use as per synopsis – including margin.

4.3.1 Report localization methods and techniques – dye and materials used, volume of dye (methylene blue, ICG etc.), other materials such as microcoils, hook wires etc. Details regarding these techniques will be collected.

4.3.2 Collect data on intraoperative percutaneous localization time and duration of total surgical procedure.

4.3.3 Record nodule characteristics, including location in the lobe, distance from pleura, distance from surface of skin to target, morphological appearance, solid vs. ground glass etc.

4.3.4 Record weight of excised tissue and margin.

4.3.5 Report type of surgical resection performed (segmentectomy or wedge) and resection technique (VATS, RATS, thoracotomy).

5. SUMMARY OF REGISTRY DESIGN

PLOTS is a multicenter, post-approval study of the SPiN System™ in percutaneous localization. It's an open-label registry study practically focused on the expedient intraoperative localization and removal of small pulmonary nodules in subjects undergoing lung nodule resection. The study will aim to collect data from 70-100 patients at approximately 5 thoracic surgery sites distributed across the U.S. Each site is expected to enroll a minimum of 6 subjects. Enrollment will be monitored and will stop once sufficient data has been collected.

All post-surgical treatment decisions and clinical assessments will be at the discretion of the patient's cardiothoracic surgeon or clinician per usual care, not be mandated by registry design. Please refer to Table 2 for a diagram of the study flow.

6. DEVICE DESCRIPTION

Definition of medical device: under 21 U.S.C. 321(h), a medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is:

- recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

The SPiN System is designed to help guide the physician with electromagnetic navigation while using a bronchoscope to help visualize nodules, and a transthoracic needle to reach nodules in a single procedure setting. Veran System components include an electromagnetic field generator, a locatable sensor probe that allows navigation through the bronchi/chest wall and computer software that creates virtual images for procedural guidance.

In this study, the Veran System and sampling instruments will be used according to the associated Instructions for Use (IFU) (Appendix A) and in accordance with approved product labeling. The SPiN System utilized in this study will have SPiN Drive and SPiN Planning software version 4.0 or higher. Minor software updates are allowed if performed at all study sites within a reasonable timeframe. Under this circumstance, appropriate Investigator/site training must follow a software update and must also be noted in each investigator's study binder.

6.1 Materials Used

Veran Medical Technologies manufactured medical devices used in this study are SPiN Thoracic Navigation System™ with an assortment of needles having guidewires, SPiN Perc™ kit, and introducer and localization needles.

Table 6.1	
Device Name	SPiN Thoracic Navigation System™ and tools
Type	Medical Device
Device Level	II
Status	Approved Medical Device
Procedural Registry	Refinement of localization technique
Sourcing	Veran Medical Technologies
Current/Former Name(s) or Alias(es)	Veran Medical Technologies Aliases

1. The Veran SPiN Thoracic Navigation System™ and SPiN Perc™ Kit were cleared to market by the U.S. Food and Drug Agency (FDA) under 510(k) (K170023).
2. 510(K) Number K122106 Device Name. SPIN DRIVE ALWAYS-ON TIP TRACKED STEERABLE CATHETER ALWAYS-ON TIP TRACKED SHEATH ALWAYS-ON TIP TRACKED ASPIRATION NEEDLE.
3. Please find the instructions for use and the package labeling in Appendix A.
4. Transthoracic training and usage of the needles and System were covered in didactic, peer-to-peer, site initiation visit, and cadaver course trainings.

AOTT Localization Needles (Thoracic)

INS 5610 SPiN Perc™ Localization Needle 19 gu x 105mm with 1cm marking zone.
INS 5611 SPiN Perc™ Localization Needle 10 gu x 105mm with 2cm marking zone.

SPiN Perc™ Kits

INS-5600 SPiNPerc™ Biopsy Needle Guide Kit (Includes INS 5029).
INS 5620 SPiNPerc™ Biospy Needle Guide Kit (20 cm).

SPiN System and Components

SYS-0185 SPiN Planning Laptop.
SYS-1500 SPiN View System.
SYS-3000 IG4 System.
SYS-4000 SPiN Thoracic Navigation System 120 volts 60 hz (US).

6.2 Other Medical Devices

Devices (not manufactured by or for Veran Medical Technologies) used in this study are expected to include 1cc – 3cc Luer lock syringes, Olympus MP-160 or BF-190 bronchoscope, and microcoils and fiducials.

6.3 Instructions for Use

Instructions for use of the medical device are provided (Appendix A). All device deficiencies (including malfunction, use error and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation, following the instructions and form found in section Appendix C.

7. PRIOR CLINICAL DATA

Current recommendations from the American College of Chest Physicians (ACCP) evidence-based guidelines for the management of pulmonary nodules begin with examination of the nodule, and an estimation of the clinical probability that the nodule is malignant and evaluation of surgical risk. For subjects with a high probability of cancer (>60%), diagnosis by biopsy and resection are recommended. More than 40% of lung targets are not accessible by conventional bronchoscopy due to their location, with contributing factors including the small diameter of the airways, lack of an airway leading to a nodule and maneuverability difficulties (Rivera et al, 2003; Alberts and Colice, 2003).

The ability to identify and to obtain diagnostic tissue from PPNs has been evaluated in various clinical trials using a variety of techniques. The results over time are variable and do warrant further investigation. Techniques such as diagnostic bronchoscopy alone, and then in comparison with EMN-guided bronchoscopy, EMN-TTNA, and r-EBUS were studied in the large, multicenter registry-based clinical effectiveness study (AQuIRE Registry) (*ibid..).* The AQuIRE registry had a primary objective to measure and identify the determinants of diagnostic yield for bronchoscopy in patients with peripheral lung lesions. Secondary outcomes included diagnostic yield of different sampling techniques, complications, and practice pattern variations. Subjects were enrolled at 15 centers having 22 study physicians between 2009-2014, and the registry was funded by the CHEST organization.

Ost *et al.* reported unexpectedly low diagnostic yields for electromagnetic navigation.

Regarding the low EMN rate, one AQuIRE PI noted (Semaan R.W., 2016):

> "…more than 98% of the EMN cases were performed with a single system (Medtronic, Minneapolis, MN) that lacks additional capabilities, including TTNA under EMN guidance. Since the completion of enrollment in the AQuIRE study, newer EMN technologies have been developed and now allow for a navigational transthoracic approach."

Ost replied in response that: "In such a scenario, the real question is not whether sensitivity will improve but, rather, by how much sensitivity will improve, and whether that improvement is worth the attendant increase in risk."

Acknowledging the Hopkins observation that that SD was used in almost all EMN cases, Ost writes:

> "They point out correctly that 98% of the cases in the AQuIRE registry were performed with SuperDimension (Medtronic, Minneapolis, MN). I concur that not all EMN systems are the same. There are substantive differences in the imaging and algorithms used between these two systems. Veran uses both inspiratory and expiratory films, whereas SuperDimension does not. Respiratory motion can affect nodule location significantly (2). The data in the AQuIRE registry do not provide insight into how Veran might perform in terms of bronchoscopic yield. On the basis of the difference between EMN systems, I agree that separate studies for the Veran system are warranted. "

As these (AQuIRE) were percutaneous cases using early EMN-guidance, the results of this registry may likewise provide insight into impacts of technological advances. The AQuIRE registry had a primary objective to measure and identify the determinants of diagnostic yield for bronchoscopy in patients with peripheral lung lesions. Secondary outcomes included diagnostic yield of different sampling techniques, complications, and practice pattern variations.

- The AQuIRE registry reported poor diagnostic yields for multiple modalities
  - Bronchoscopic alone: 53.7%
  - r-EBUS when used alone: 57%
  - EMN Yield when used alone was 38.5% (98% of cases were SuperDimension technology)

Of these, 312 subjects in the trial underwent transbronchial biopsy. Using bronchoscopy alone, the diagnostic yield was reported as 63.7%. In earlier work, the average diagnostic yield for peripheral lung lesion biopsy performed with conventional flexible bronchoscopy was reported to be 69% for peripheral lesions greater than 20 mm and 33% for peripheral lesions less than 20 mm, (Mazzone *et al*, 2002; Riveria *et al*, 2003; Schriebner and McCrory, 2003).

Results from studies involving procedural guidance technologies such as electromagnetic navigation (EMN) and radial endobronchial ultrasound (radial EBUS) have also been reported (Ost *et al*., 2016). Diagnostic yield was reported at 57% with r-EBUS alone, 47.1% with EMN combined with r-EBUS. In another recent study published in the New England Journal of Medicine, a total of 639 subjects underwent bronchoscopy for suspected lung cancer and of those bronchoscopic examinations, 43% were nondiagnostic, including in 25% (120 of 487 subjects) in whom lung cancer was ultimately diagnosed (Silvestri *et al*, 2014). As a result of published yields showing an unacceptable yield for peripheral bronchoscopy, ACCP guidelines recommends that nodules without a CT-bronchus sign should be pursued with EMB-TTNA (Rivera *et al*, 2013).

A prospective, single center pilot study evaluated the safety, feasibility, and diagnostic yield of staged approached for taking biopsy samples in a single procedure setting (Yarmus LB et al., 2016). In this study, enrolled subjects (n=24) underwent EBUS for lymph node staging, followed by EMN-bronchoscopy, and EMN-TTNA. The researchers report a diagnostic yield of 83% for EMN-TTNA alone, and 87% when combined with EMN-bronchoscopy. The diagnostic yield increased to 92% when combined with EBUS. There were five (21%) pneumothoraces of which two (8%) required chest tube placement. No bleeding events were observed. The researchers conclude that the results demonstrate an acceptable safety and feasibility profile.

8. RISKS AND BENEFITS

PLOTS is a registry documenting small lung nodule localization techniques used by thoracic surgeons for patients just prior to lung resection. The localization PPNs with dye injection and/or microcoils is a standard medical procedure physicians complete prior to the resection procedure. All procedures represent the clinical standard of care provided by thoracic surgeons to their patients. The following section documents the risks and benefits of Registry participation, as well as the published clinical rates of complications as they are known.

The risks associated with the localization procedure are noted, as well as the use of the device. If approved devices will be used as part of the research, each site may be asked to confirm that the device(s) they are using are being used within their approved labeling

The SPiN Thoracic Navigation System™ and its accessories are marketed for use as tools in the diagnosis and treatment of lung cancer. All devices used in this study are commercially available and there are no anticipated risks beyond those already associated with early lung cancer diagnosis and surgical treatment procedures in clinical practice.

Data, including safety data, will be collected from each subject's nodule localization procedure. The surgical procedure is not experimental in this 510(k)-marketed device that is being used within its approved labeling. Safety data will be summarized and reported from the localization procedure.

8.1 Registry Data Collection – Risks and Benefits

Registry Risks: Every effort will be made to protect the privacy of research subjects. Subject names and protected health information (PHI) will be kept confidential to the extent possible and as required by HIPAA. All records and data related to the study will be maintained in a secure protected space, with access restricted to study personnel or individuals designated by study personnel who (i) need access to the information to fulfill the terms and obligations of the Coordinating Site or the Sponsor under the Protocol and (ii) are under the same obligations as study personnel to keep the information confidential. It is an open-label study, and each study site will use its own portal only. There are software firewalls in place to prevent site personnel from seeing data from other investigative sites.

Registry Benefits: Subjects will not receive any direct benefit as a result of their participation in the registry. However, information contained within the registry will be used for research studies directed at improving our knowledge and treatment of very early lung cancer diagnosis, screening, and treatment. Identifying best practices for use in small nodule localization may benefit patients with early lung cancer in the future.

8.2 Procedural Data Collection – Risks and Benefits

Procedure-Related Benefits

The Veran ENB SPiN Thoracic Navigation System™ for lung cancer and the SPiN Perc™ Kit (Veran System) were cleared to market by the U.S. Food and Drug Agency (FDA) under 510(k) (K170023). The Veran System is designed to help guide the surgeon with electromagnetic navigation while manipulating small pulmonary nodules. Early detection (and removal) of lung cancer relies upon the precise identification and prompt removal of pulmonary nodules. Deep pulmonary nodules represent a particular technical challenge for surgeons, due to their accessibility. SPiN System biopsy tools are capable of integrating information from imaging devices into real-time visualization, allowing for targeted percutaneous localization of small PPN's. Optimization of this technical localization procedure may result in more accurate identification of small tumors in lung tissue, when used by a skilled, trained surgeon or physician.

Procedure-Related Risks

Reported radiation exposures to the patient from the low dose helical CT procedure are comparable to current practice. No additional procedural risks are anticipated to be introduced.

8.2.1 Anesthesia – Lung Resection Procedure

Sedation and the act of passing a bronchoscope into the airway introduce medical risks. Older adults, or those with serious medical problems, particularly those undergoing more extensive procedures, may be at increased risk of postoperative confusion, pneumonia, or even stroke and heart attack. To mitigate the risks of anesthesia, anesthesiologists or anesthesiology nurses and/or a respiratory therapist typically monitor all patients during the procedure per their institutional protocols and training. In addition, oxygen saturation (using pulse oximetry), respiratory rate, blood pressure, ECG, and heart rate are typically continuously monitored. Patients are not released until they are fully awake and medically stable.

The benefits of anesthesia are that subjects will not feel or remember the pain of the surgical procedure.

8.2.2 Bronchoscopy – Lung Resection Procedure

The greatest risks from bronchoscopy, used as a step to align ("register") the subject's day of surgery CT with the subject's current position on the surgical table, are related to sedation and to the act of passing a bronchoscope into the airway. To mitigate the risks of bronchoscopy, subjects will be under general anesthesia. Subjects are typically monitored during this

procedure. In addition, oxygen saturation (using pulse oximetry), respiratory rate, blood pressure, ECG, and heart rate are continuously monitored. Patients are typically hospitalized following lung surgery for approximately days in the US and released when medically stable.

8.2.3 Trans-thoracic Nodule Localization – Registry Procedure

The risks associated with trans-thoracic nodule localization are bleeding and pneumothorax,

The measures to mitigate the risks are the same for all surgical procedures. Patients are given supplemental oxygen and their oxygen level is continuously monitored using pulse oximetry. A nurse or physician continuously monitor patients' ECG, heart rate, blood pressure, and blood oxygen during the procedure.

9. RESEARCH METHODS AND DATA COLLECTION

In this study, the "lung resection and after care protocol" is determined by each investigator's current practice, with an outline provided in the registry to explain the context for the type of data collection performed in this patient population. The medical device is being marketed for and used within its intended use.

Localization methods and outcomes, and data related to the nodules, diagnosis, and the setting of the planned clinical intervention of nodule removal will be recorded. Data will be collected according to descriptions below, Table 1 and Figure 1.

Collected data include brief medical history, smoking history, demographic characteristics, radiographic characteristics, procedural characteristics, crossover to other procedures, and adverse events, as follows:

- *Radiographic Characteristics*:

  The location of the target nodule (side, lobe and segment, i.e. right upper lobe anterior segment, etc.) will be determined and recorded. The radiographic information collected from CT will include size of the nodule (longest axis), distance from a visible bronchus, and distance from the pleural surface perpendicular to the nodule.

- *Procedural Characteristics*:
  Collected procedural information will include the distance of target from pleura nodule statistics (volume, RESIST diameter, maximum, minimum, and effective diameter), and target motion. The duration of the localization procedure will also be recorded.

- *Crossover to Other Procedures:*

All procedures performed to aid in the surgical management of patients – will be noted. Wedge resection, segmentectomy, and lobectomy. The type of initial surgery planned, and the eventual surgery done, will both be collected.

- *Adverse Events:*
  All device and/or procedure related adverse events will be recorded for the study localization procedure. Events will be collected from the initiation of the localization procedure to the start of the wedge resection procedure. Study sites will report localization-related adverse events and complications to their IRBs according to institutional requirements. These will be recorded.

9.2 Primary Efficacy Objective: Successful Percutaneous Localization of PPN

This is defined as the percentage of subjects in whom the nodule is successfully localized and removed in the first resected specimen. A pathological specimen with clear margins will count as a successful localization.

To evaluate the accuracy of percutaneous nodule localization using the SPiN Thoracic Navigation System™ and its accessories, by recording the percentage of successful nodule resections that result in the complete removal of the patient's nodule, with at least a one cell perimeter and negative margins. The diagnostic yield is calculated as the percentage of patients who have intra-operative localizations resulting in complete removal of nodule, divided by the total number of evaluable subjects.

Confirmation of Diagnosis
Surgical pathology results will determine the outcome of the primary endpoint. If the patient has follow-up imaging that shows a decrease in size or resolution of the nodule, the nodule will be determined to be of benign etiology if the study pathology yields a benign diagnosis (granuloma, inflammation, fibrosis, infection). To verify final diagnosis, a copy of the final pathology report will be de-identified and provided by the site. The pathology findings will then identify the case as either benign or malignant. Whether a benign or malignant diagnosis is made, the primary endpoint is met.

If Margins are Intact
If the nodule has intact margins as described by the pathology report. Explicitly, a perimeter of at least one cell around the nodule contain cells that are all non-malignant. This plus the nodule sample verifies that the entire nodule was removed. The pathology findings will then identify the case as either benign or malignant.

Crossover Cases
It is anticipated that there will be cases where the wedge is positive for malignancy and the deep margin also will be positive. In these cases, the surgical plan may change from a planned wedgectomy into a completion lobectomy or segmentectomy. If the nodule is fully removed

(having at least a cell's margin of non-malignant cells in these cases, then the primary endpoint is met. The pathology findings will then identify the entire case as either benign or malignant, and the primary endpoint is met.

Margins for Crossover Cases
If the nodule is fully removed in crossover cases, then the primary endpoint is met. The nodule may be removed per the surgeon's judgement. The pathology findings will then identify the entire case as either benign or malignant, and the primary endpoint is met.

If Diagnosis is Non-malignant
If the nodule is deemed non-malignant, cells are identifiable, then the positive box for diagnosis is checked, and:

- The nodule must have an intact margin of a cell as a perimeter to be diagnostic.
- The type of nodule (ground glass opacity, etc.) is collected from the pathology report.

The pathology findings will then identify the case as either benign or malignant.

9.3 Safety Objective:

Record Safety Events During Intraoperative Percutaneous Localization Only
To collect and evaluate the safety of nodule localization, including incidence and severity of localization-procedure related adverse events (AEs) and serious adverse events (SAEs) that occur during the localization procedure.

Baseline/Enrollment
All patients will be provided with information about the registry and will sign the informed consent form before any registry-related assessments are made. The following data will be collected at baseline for all enrolled patients:

- To be collected at baseline visit: Review of inclusion/exclusion criteria.

Localization Period

- The localization period begins when the needle touches the subject's skin.
- Localization ends when the localization needle is withdrawn from the subject for the final time.
- Any adverse events that develop during the localization procedure will be reported.
- Bronchoscopy-related events that occur during the alignment of the CT with the patient ("registration") will be recorded.
- Percutaneous localization step, injection of dye, injection of any microcoils, etc.

The process used for AE reporting conforms to Veran Medical Technologies, Inc., standard operating procedures (SOPs) for Medical Device Reporting (MDR)(Appendix C). Training on AE/SAE/MDR reporting practices will be provided to each participating site.

9.3 Subject Enrolment and Informed Consent

Patients presenting to their physician in need of assessment or removal of peripheral pulmonary nodule(s), and who meet study inclusion/exclusion criteria, will be invited to participate. Patient enrolment will follow each participating institution's standard of care. Subjects will be approached to obtain informed consent prior to any study-specific procedure. Informed consent will take place in a private environment (e.g. patient exam room), free from distractions. The PI or study team member will approach the subject at their clinic appointment and will explain the study to qualified subjects prior to obtaining consent. All individuals who obtain consent (PI, Sub-investigators, and study coordinators) must have received GCP informed consent training within the past 2 years. Interviews to obtain consent will not follow any stressful situation (e.g. patient being informed he/she may have cancer) and will not be conducted if the patient has received any mind-altering medications or anesthesia. Patients will be assessed for their capacity to consent by the ability to show comprehension of the procedure, ask appropriate questions, and appear properly oriented.

The PI will confirm subject eligibility. Patients who sign the informed consent form will be considered enrolled. A signed copy of all consents and the HIPAA authorization document will also be given to consenting subjects.

Patients who complete the localization procedure will be included within the analysis population. Reasons for study withdrawal will be recorded. Each patient's participation in this study is approximately 6 weeks baseline through subject's discharge from hospital following lung surgery.

9.4 Withdrawal of Subjects

Following informed consent, subjects withdrawn from the study prior to the localization procedure due to patient withdrawal of consent or at the discretion of the investigator will be considered withdrawn. In the case of investigator withdrawal, the reason for early withdrawal will be documented. Data collected from all treated patients undergoing localization will be included within the analysis population.

9.5 Screen Failures

Subjects who provide informed consent but are determined to be ineligible prior to the index procedure will be considered screen failures. The reason for screen failure will be documented. The assigned subject ID for the subject will not be re-used.

9.6 Pre-procedure Chest CT Scan Evaluation

After informed consent is obtained, the patient's most recent chest CT scan or chest x-ray will be deidentified and securely downloaded and saved. If subjects have multiple pulmonary nodules, the site PI will identify the target nodule.

9.7 Non-contrast Chest CT

It is recommended by the manufacturer that the subject receives a non-contrast chest CT scan be performed on the same day as the procedure as a clinically indicated procedural planning tool (Veran Appendix B – technical description of CT parameters). Otherwise, a chest CT scan from within the past 15 days may also be used when it is consistent with these parameters.

9.8 General Anesthesia

Patients will undergo the procedure under general anesthesia.

9.9 Nodule Localization

The bronchoscope (Olympus MP-160 or BF-190) will be introduced into the airway. A Veran tip tracked instrument will then be introduced into the working channel of the bronchoscope and utilizing standard Veran System navigation-matching protocols, the main and secondary carinas are identified using the tip tracked instrument to confirm that the Veran System is properly matched to the airway defined by accurate matching of the main and secondary carina. This allows the system to align the CT with the patient's current position.
Following registration, a sterile field is created on the chest wall as identified by the Spin Perc planning software and the area is prepped and draped. A tip tracked needle, such as one of the Veran localization needles or the Veran tip tracked Spin Perc needle introducer, is selected. The surgeon advances the needle trans thoracically into the nodule, under Veran EMN guidance, to the nodule. The nodule is localized percutaneously by marking with dye using an assortment of tools designed for this purpose (Section 5.1), adding microcoils or fiducials, etc.

Data Collected: patient position, registration, volume of dye, type of dye, use of microcoils or fiducials.

The surgeon then continues to wedge resection, and the registry portion of the procedure is completed.

9.10 Study Discontinuation

The following data will be recorded as available from any enrolled subjects who withdrew consent during the Registry:

- SAEs/AEs - Method of treatment, severity, etc.
- Concomitant medications including dosages
- Reason for withdrawal

10. COMPLAINT AND SAFETY REPORTING

Principal Investigators were taught to use FDA 3500A MedWatch (Appendix C) and were taught to fill those out during the investigator meeting, for relevant SAEs and also for medical device complaints. This registry's primary safety objective is to collect localization-related safety events in patients undergoing wedgectomy.

The Medical Device Reporting (MDR) regulation (21 CFR 803) contains mandatory requirements for device user facilities (including hospitals, surgical facilities and other) to report certain device-related serious adverse events and product problems to the FDA. These are described in further detail below.

- User facilities must report a suspected medical device-related death to both the FDA and the manufacturer within 10 days.
- User facilities must also report a medical device-related serious injury to the manufacturer (Veran Medical Technologies, address below).
- In addition, each IRB and institution may have its own policies regarding the content, format, and timing for the reporting of SAE information.

Each investigator is responsible for fulfilling these duties. Please report device serious adverse events to Veran as noted below on form 3500A (Appendix C):

Email: vsupport@veranmedical.com
Email: plots@veranmedical.com

10.1 Complaint Reporting

A device deficiency is an inadequacy of a medical device related to its identity (e.g. labeling), quality, durability, reliability, safety or performance, such as malfunction. It can also include a broken needle. It is important to Veran Medical Technologies to be aware of and remedy any device deficiencies. Please submit complaints or product problems to Veran Medical Technologies, using form 3500A (Appendix C).

User facilities are not required to report a device malfunction to the FDA. They can voluntarily inform the Agency of such product problems through MedWatch, using form 3500A (Appendix C).

Please report device deficiencies to Veran as noted below on form 3500A:

Email: vsupport@veranmedical.com
Email: plots@veranmedical.com

10.2 Safety Reporting

All SAEs and device deficiencies related to the Veran system or its instruments are also to be reported directly to Veran as follows: (please send to **vSupport**, and Cc: the **PLOTS** email)

Email: vsupport@veranmedical.com

Email: plots@veranmedical.com

For any FDA-reportable event, please also forward to the following for awareness:
Contact: Nathan Hunt
Phone: (314) 334-5363
Email: Nathan.Hunt@veranmedical.com

Safety events from the localization procedure only will be collected in the registry (please refer to Appendix B for all data elements collected in Registry).

This study is being conducted under 21 CFR part 50[1] (https://www.ecfr.gov/cgi-bin/textidx?SID=244dabc113521b0a851a5db147554fdd&mc=true&node=pt21.1.50&rgn=div5) using a 510(k)-cleared device system. The exemption in 21 CFR 812.2(c)(2) applies to this study, where the device is substantially equivalent to its predicate, and the device is being used in accordance with its labeling.

Study sites are likewise responsible to report adverse events and complications to their IRBs according to institutional requirements.

10.3 Adverse Events – Data Collection for Localization Events

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. Note: Pre-existing conditions are not considered to be adverse events unless there is a change in the nature or severity of the condition.

We will collect data on the localization adverse event through subject discharge from hospital. Principal Investigators were taught to use FDA 3500A MedWatch (Appendix C) and were taught to fill those out during the investigator meeting, for relevant SAEs and also for medical device complaints. This registry's primary safety objective is to collect localization-related safety events in patients undergoing localization prior to wedgectomy.

The Medical Device Reporting (MDR) regulation (21 CFR 803) contains mandatory requirements for device user facilities (including hospitals, surgical facilities and other) to report certain device-related serious adverse events and product problems to the FDA. These are described in the forms in Appendix C, and the FDA's Guidance for User Facilities.

- User facilities must report a suspected medical device-related death to both the FDA and the manufacturer within 10 days.
- User facilities must also report a medical device-related serious injury to the manufacturer (Veran Medical Technologies, address below).
- In addition, each IRB and institution may have its own policies regarding the content, format, and timing for the reporting of safety information.

[1] The Electronic Code of Federal Regulations (www.ecfr.gov) - https://www.ecfr.gov/cgi-bin/textidx?SID=244dabc113521b0a851a5db147554fdd&mc=true&node=pt21.1.50&rgn=div5 accessed 4/16/2019.

Each investigator or delegate is responsible for fulfilling these duties.
Please report device serious adverse events to Veran as noted below on form 3500A (Appendix C).

Please scan and send completed forms to:
Email: vsupport@veranmedical.com
Email: plots@veranmedical.com

10.3.1 Serious Adverse Event

A serious adverse event (SAE) is an adverse event that has:

1. Led to death,
2. Led to serious deterioration in the health of the subject, that either resulted in:
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the study, without serious health deterioration is not considered a SAE.

10.4 Causality – Adverse Event Relationship

The PI will assess the relationship of an adverse event to the device and procedure as follows:

- *Not Related:* No relationship appears to exist between the AE and the device and/or procedure.
- *Related:* The AE follows a plausible temporal sequence following administration of the study device and/or execution of the procedure.
- *Undetermined:* It is not possible to determine the relationship of the AE with the study device and/or procedure.

10.5 Adverse Event Outcome

The outcome of AEs will be recorded as follows:

- *Resolved:* The event is considered fully resolved.
- *Continuing:* At study exit the event is considered ongoing.

Note: Any unresolved AE ongoing past study exit will be monitored by the physician per institutional standard of care.

10.6 ADVERSE EVENT RECORDING

AEs will be documented in the applicable source documentation (i.e. medical record). Study data collection forms should capture the event diagnosis as opposed to symptoms (e.g. Infection vs. fever). The adverse events of pneumothorax and bronchopulmonary hemorrhage (including hemoptysis) will be documented as follows:

- *Hemorrhage:* Significant bronchopulmonary hemorrhage including hemoptysis will be defined as bleeding noted at the time of procedure that requires a change in the level of care (e.g. outpatient to inpatient or inpatient to ICU) or a blood transfusion or separate intervention (i.e. surgery or embolization). Severity will be classified according to CTCAE as follows:
  - *Grade 1:* Mild symptoms; intervention not indicated
  - *Grade 2:* Moderate symptoms; medical intervention indicated
  - *Grade 3:* Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g. hemostasis of bleeding site)
  - *Grade 4:* Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
  - *Grade 5:* Death

11. STATISTICAL METHODS

11.1 Sample Size

This is an observational study where no formal hypothesis is being tested, data collected during the study will be summarized using descriptive statistics. No formal sample size estimations were utilized to determine the size of the study population. Generally, demographic and other descriptive characteristics of the cohorts will be described as counts and percentages for categorical variables and as measures of central tendency (mean, median, standard deviation [SD], and range) for continuous variables. Ninety-five percent (95%) confidence intervals will be computed for measures of effect and association. In some cases, data may be summarized by demographic.

The study will have 70-100 evaluable patients from approximately 5 sites in the US who undergo percutaneous localization followed by surgical resection. Evaluable patients are those who undergo the percutaneous nodule localization procedure and meet the inclusion/exclusion criteria. Each site will be expected to enroll a minimum of 6 subjects at their site.

11.2 Data Analyses

11.2.1 General Considerations

The analysis to be performed will be described in a written and approved statistical analysis plan (SAP). No adjustments will be made for multiple comparisons. Effectiveness data will be summarized. Serious adverse events (SAEs) and adverse

events will be listed and summarized. Data collected during the study will be uploaded at the sites into Medrio and summarized and analyzed at least bi-annually.

All AE and Medical History verbatim terms will be recorded and coded using the CTCAE criteria.

11.2.2 Handling of Missing Data

The proportion of missing data will be reported for each measured variable in the study.

12. STUDY MANAGEMENT

12.1 Overall Study Management

- **Regulatory Considerations:** The SPiN System and tools are a medical device that is 510(k) exempt under 21 CFR 812.2(c)(2), which applies to the investigation. The 510(k) product is being used in accordance with the product labeling (Appendix A).
- **Subject Protection:** 21 CFR part 50; 45 CFR part 46
- **Patient Privacy:** HIPAA
- **IRB Approval:** 21 CFR part 56
- **Good Clinical Practices:** 21 CFR part 11; 21 CFR part 812
- **Site Monitoring:** Veran Medical Systems
- **MDR:** 21 CFR part 803

Investigators will be selected on the basis of their experience, training, and education. The sponsor will provide the final protocol and coordinate the review, dissemination, and approval of protocol amendments (if any). The sponsor will develop the study database and define the data collection process. Sponsor staff will collect and maintain study-related documents from participating sites (e.g. Protocol signature page, training documents, IRB approval, etc.) to create a sponsor's study file. The sponsor will develop consent form template with the expertise of study investigators, provide IRB submission assistance if required, and confirm IRB approval prior to subject enrollment.

Likewise, the sponsor will:

- Provide routine monitoring of data and protocol deviations as collected;
- Disseminate information to sites and IRBs as appropriate.
- Schedule routine meetings (e.g. teleconferences) with participating sites and develop monthly progress reports.
- Provide study-specific training for staff at participating sites.
- Perform periodic site visits to assess protocol adherence.

An executive steering committee will determine the schedule and quantity of publications and will routinely review data from the registry.

Electronic Data Capture

All data will be collected and entered into the electronic data capture (EDC) system that Veran Medical Technologies has created specifically for this purpose (Medrio®). Sites will be responsible for entering extracted patient data into a secure internet-based EDC registry database via the eCRF. Investigators and site personnel will be able to access their secure, encrypted accounts with individual usernames and passwords. Participating sites will have access to their own enrolled subjects' data only, with permissions assigned to trained study staff. All eCRFs should be completed by designated, trained personnel or the study coordinator, as appropriate. The eCRF should be reviewed, electronically signed, and dated by the Principal Investigator. All changes or corrections to eCRFs will be documented in an audit trail with an adequate explanation made to explain the reason for the change, a signature, and a time/date stamp.

12.2 File Retention and Archiving

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the investigator agrees to keep records, including the identity of all participating patients, all original signed ICFs, copies of all case report forms (CRFs), SAE forms, site files, investigator information, source documents, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes). The records should be retained with the study binder.

Each site will receive a study site file at study initiation which contains all documents necessary for the conduct of the registry and is updated throughout the study. This file must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least 5 years after completing participation in the study. Documents to be archived include site regulatory files including IRB approvals, the subject enrollment log and the signed ICFs. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify the Sponsor.

If these files are filed electronically, they must follow electronic document archival practices, contain a backup file on the same media, and also the ability to read the files for 5 years.

12.3 Data Management

High data quality standards will be maintained, and processes and procedures will be utilized to ensure that the data are as clean and accurate as possible when presented for

analysis. Data quality will be enhanced through a series of programmed or manual data edit checks that automatically detect out-of-range or anomalous data.

12.4 Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. Major (i.e., substantial, significant) amendments will usually require submission to the relevant IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed at each participating site and will be submitted to the relevant IRB or regulatory authorities where required by pertinent regulations. Any amendment that could have an impact on the patient's agreement to participate in the study requires the patient's informed consent prior to continued participation in the study.

12.5 Study Governance

An executive steering committee of 4-6 members will be established, drawing from the investigators enrolling patients into this study. This committee, with the sponsor, will review the protocol and oversee the study design. The committee will also recommend meetings and topics for abstracts and papers to be submitted for presentation and publication. All investigators will have access to the data for their individual site; however, only the sponsor or its designee shall have access to the entire, multicenter data set. The ESC may review the de-identified data, for purposes of oversight and also for publication. Any requests for publication of individual site data will be submitted to the committee for review and consideration; the committee recommendation will be submitted to the company for consideration.

All data generated from this study will be the exclusive property of Veran Medical Technologies, Inc.

12.6 Publication Policy

Any publication of the results from this study must be consistent with the Sponsor's publication policy and guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated April 2010 (ICMJE 2010). The rights of the Investigator and of the Sponsor regarding publication of the results of this study/registry are described in the Investigator contract.

13. PROTOCOL COMPLIANCE

No amendments to the protocol are permitted without prior written approval from the Lead Investigator, Veran and the associated IRB. Deviations to the protocol are not allowed, except in the case of an emergency, or for the protection of the life or physical

well-being of the subject. Investigators are responsible for reporting all protocol deviations to Veran in writing as soon as reasonably practicable and to their IRB per the local reporting policy. Unless otherwise notified in writing, investigators shall provide a written report to Veran's Director of Clinical Studies describing all protocol deviations in full and shall cooperate with Veran to provide any additional information upon request in a reasonable and timely manner.

14. DATA STORAGE AND MAINTENANCE

This study will utilize an electronic database. Prior to study initiation, the PI and staff will receive training to ensure that all personnel fully understand the protocol, data collection, and any other study related issues or documents. Data will be collected from patient's charts, EHR, medical imaging, and the Veran System. The Registry database will belong to Veran Medical Technologies.

Electronic Data will be entered and stored in the secure Medrio® database created for this study. Medrio® is a web-based application designed exclusively to support data capture for research studies. It provides an interface for data entry, audit trails, procedures for importing data from external sources, data features such as branching logic and calculated fields, and automated export procedures for data downloads to common statistical packages such as SAS.

Each PI will review the collected study data, which will become part of the subject's medical record and research record. Any clinical follow-up or repeat procedures will be dictated by the patient's physician based on clinically relevant data and will not be influenced by enrollment into this study.

To protect subject confidentiality, the data entry/portal tool will receive all patient data as de-identified through use of the study data codes. All information and data related to this study will be stored in a secured, locked cabinet at Veran Medical Technologies, and also at each investigator's site.

Access to this study data is restricted to the Sponsor and to study personnel alone, and controls include encryption and user-id and password-protected databases.

Registry documentation and paperwork will be stored at each Principal Investigator's site in a locked file cabinet. Registry records will be retained for 5 years after the completion of the registry. After that period of time, all individual patient information will be managed according to the policies of the PI's institution.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Guiding Principles and Regulations

To ensure the quality and integrity of research, this study will be conducted under Good Clinical Practices (GCPs) issued by the FDA.

Specifically, the study will be conducted in compliance with:

US FDA Title 21 CFR Part 50 – Protection of Human Subjects, and
US FDA Title 21 CFR Part 56 – Institutional Review Boards;
Health Insurance Portability and Accountability Act of 1996 (HIPAA).
US FDA Title 21 CFR Part 11 – Electronic Signatures.
US FDA Title 21 CFR Part 803.
US FDA Title 21 CFR 812; 21 CFR 812.2(c)(2) 510k Exempt Medical Device.
IRB approval and informed consent is also required for research under 45 CFR 46.

15.2 Site Required Documents

In addition to the standard site qualification documents, prior to the enrollment of any patients in the study, the following documents must be provided by the site to the Sponsor (or their designee):

- Copy of the IRB approval letter for the protocol and informed consent (all written information provided to the patient must be approved by the IRB)
- Copy of the IRB-approved informed consent document to be used
- Copy of the protocol sign-off page signed by the investigator
- Fully executed site agreement (clinical trial agreement)

This is a post-marketing study conducted within approved labeling for a marketed 510K device (and not an experimental device). An investigator's meeting and training sessions about localization techniques. A cadaver session was also held to practice localization techniques as part of the investigator's meeting.

15.3 Patient Information and Informed Consent

An ICF must be signed by the patient before his or her participation in the study. The medical file for each patient should document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed ICF must be provided to the patient. All signed and dated ICFs must remain in each patient's study file and must be available for verification by study monitors at any time.

The ICF should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the

willingness of the patient to participate. For any updated or revised ICFs, the medical file for each patient should document the informed consent process and that written informed consent was obtained for the updated/revised ICF for continued participation in the study.

15.4 Patient Confidentiality

In order to maintain patient confidentiality, each patient will be assigned a unique patient identifier upon study enrollment. This patient identifier will be used in place of patient name and or initials for the purpose of data analysis and reporting. Medical record number or other local reference identifiers are not collected as part of the database. All parties will ensure protection of patient personal data and will not include patient names on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local US regulations, patients will be informed about data handling procedures and asked for their consent. Data protection and privacy regulations will be observed in capturing, forwarding, processing, reporting, and storing patient data. Every effort will be made to protect participant confidentiality.

The database will be housed at Medrio in a physically and 21 CFR part 11 logically secure computer system maintained Medrio with a written security policy. The system meets approved established standards for the security of health information and is validated. The system also meets the standards of the International Conference on Harmonisation (ICH) guideline E6R2 regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained.

15.5 Independent Ethics Committee/Institutional Review Board

Consistent with local regulations and prior to enrollment of patients at a given site, the study protocol will be submitted together with its associated documents (e.g., ICF) to the responsible IRB for its review. Patient enrollment will not start at any site before the Sponsor has obtained written confirmation of a favorable opinion/approval from the relevant central or local IRB. The IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given that clearly identifies the study, the protocol version, and the ICF version reviewed.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IRB in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant IRBs during the course of the study in accordance with local regulations and requirements. It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and ICFs, and other relevant documents, if applicable, from their local

IRB and provide documentation of approval to Veran Medical Technologies. All correspondence with the IRB should be retained in the Investigator File.

Should the study be terminated early for any unanticipated reason, the investigator will be responsible for informing the IRB of the early termination.

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APPENDIX A – INSTRUCTIONS FOR USE

APPENDIX B – VERAN CT SCAN

APPENDIX C – SAFETY AND COMPLAINT REPORTING FORMS