Official Title: **R**obotic versus **E**lectromagnetic Bronchoscopy for Pulmonary **L**es**I**on **A**ssessme**NT**: the RELIANT trial.

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Title: Robotic versus **E**lectromagnetic Bronchoscopy for Pulmonary **L**es**I**on **A**ssessme**NT**: the RELIANT trial.

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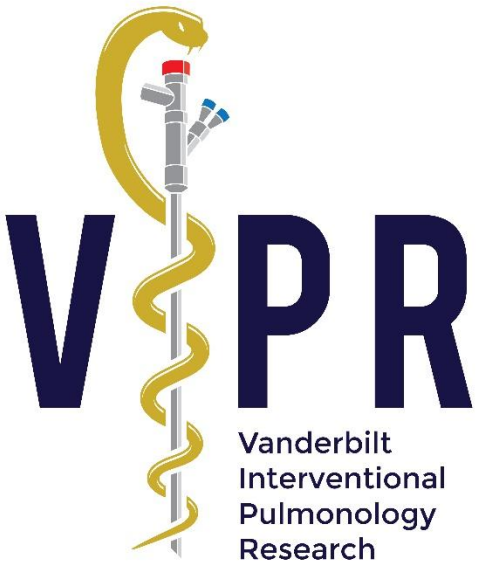

Version Date: 3/1/2024

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PROTOCOL SYNOPSIS

Title	**R**obotic versus **E**lectromagnetic Bronchoscopy for Pulmonary **L**es**I**on **A**ssessme**NT)**
Short title	RELIANT
Primary study objective	To compare the diagnostic yield of the Ion™ Endoluminal System (shape sensing catheter bronchoscopy, SSCB) to that of the ILLUMISITE™ Platform (electromagnetic navigational bronchoscopy, EMN) in patients undergoing bronchoscopy with planned biopsy of a peripheral pulmonary lesion.
Study devices	Ion™ Endoluminal System (SSCB); ILLUMISITE™ Platform (EMN).
Design	Single center, open label, pragmatic, non-inferiority, cluster randomized controlled trial.
Study centers	Vanderbilt University Medical Center
Number of clusters	N=202, to be increased if necessary
Inclusion criteria	1. ≥ 18 years of age at time of bronchoscopy. 2. Scheduled for navigational bronchoscopy for the evaluation of a peripheral pulmonary lesion.
Exclusion criteria	1. Enrolled in a different study requiring use of one specific platform 2. Subject declines to participate.
Primary endpoint	1. The primary endpoint will be diagnostic yield obtained from Ion™ or ILLUMISITE™ procedures, defined as the proportion of procedures that result in acquisition of lesional tissue. Lesional tissue: histopathological findings present that readily explain the presence of a pulmonary lesion.
Secondary endpoints	1. Duration of the procedure
Exploratory endpoints	1. Need for additional diagnostic procedures 2. Radiation exposure 3. Diagnostic accuracy at 12-months post-biopsy
Safety outcome	1. Rate of complications (including pneumothorax, bronchopulmonary hemorrhage, respiratory failure, anesthetic complications)
Subject follow-up	Patients without malignancy present on biopsy will be followed for up to 12 months as clinically required per standard of care.
Statistical methodology	We assume the diagnostic yield for EMN is 80%. The non-inferiority margin is set at 10%, cluster size of 2, and no intracluster correlation, we need 202 clusters (targeting 425 subjects to reach 202 per arm) to have an 80% power to conclude noninferiority at one-sided type I error rate set at 5%.
Interim analysis	There will be no interim analysis

GENERAL STUDY INFORMATION

Title: Na**v**igation **R**obotic versus **E**lectromagnetic Bronchoscopy for Pulmonary **L**es**I**on **A**ssessme**NT (RELIANT)**

Protocol Version Number and Date:

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 Drug Administration ("FDA") regulations and statutes. The study site shall only allow individuals who are appropriately trained and qualified to assist in the conduct of the study.

BACKGROUND AND SIGNIFICANCE

Peripheral pulmonary lesions (PPLs) are often biopsied to assess for the presence of infection, inflammation, or malignancy. Tissue can be acquired in a variety of ways: surgical resection, percutaneous transthoracic needle biopsy, or bronchoscopic biopsy. Bronchoscopy is commonly pursued to determine PPL etiology, with over 500,000 performed annually in the US alone. Advanced imaging and navigational guidance systems are required to accurately approach small peripheral lesions bronchoscopically (1, 2). A variety of navigational technologies are currently available, including electromagnetic navigational bronchoscopy (EMN), virtual bronchoscopy, thin and ultrathin bronchoscopes, and endobronchial ultrasound. No comparative data exist regarding the relative performance of these competing technologies, which are all considered standard of care and currently used interchangeably based on personal preferences and availability (2).

EMN platforms dominate the current navigational bronchoscopy market (2). The largest prospective multicenter study assessing EMN performance showed a diagnostic yield of 73% (3). The more recent addition of intraprocedural digital tomosynthesis has been reported to

increase EMN diagnostic yield to 75-83% (4-6); this feature is included in the ILLUMISITE™ electromagnetic navigational bronchoscopy platform (Medtronic, Minneapolis, MN, U.S.) and is labeled “fluoroscopic navigation”.

Recently, the FDA cleared a novel navigational technology: shape-sensing catheter bronchoscopy (SSCB), via the 510(k) pathway (7, 8). This pathway requires a technical demonstration of safety and efficacy similar to that of an existing predicate device but does not usually require clinical data. Since market release in 2019, single-center prospective cohort data have emerged suggesting SSCB diagnostic yield is comparable to EMN (9), but no high-quality comparative data exist regarding the relative performance of these two technologies. Despite this important knowledge/data gap, SSCB has become a popular platform in the advanced bronchoscopist community. High-quality comparative data are required to inform optimal patient care. Additionally, EMN and SSCB platforms are considered capital purchases, each costing hundreds of thousands of dollars. Hence, it is also important for health care systems to have high quality data as they consider device purchases. VUMC currently utilizes both SSCB and EMN and they are used interchangeably in our two operating rooms. Patients are typically assigned arbitrarily to procedures using either platform based on operating room availability.

Thus, we propose a randomized controlled study to test the hypothesis that the diagnostic yield of SSCB is not inferior to EMN in patients undergoing bronchoscopy to biopsy a PPL.

HYPOTHESIS AND STUDY OBJECTIVE(S)

Hypothesis

We hypothesize that the diagnostic yield of the Ion™ Endoluminal System (SSCB) is not inferior to the ILLUMISITE™ Platform (EMN) in patients undergoing bronchoscopy for biopsy of a PPL.

Objectives

This is an investigator-initiated, non-inferiority, open labeled, cluster randomized controlled trial. Our primary objective is to compare the diagnostic yield of the Ion™ Endoluminal System (SSCB) to the ILLUMISITE™ Platform (EMN bronchoscopy) in patients undergoing bronchoscopy for PPL evaluation. Our secondary objective is to compare the rate of complications, procedure time, radiation exposure, absence of malignancy at 12 months, and need for additional procedures between these two bronchoscopic modalities.

METHODS

General Study Design

This is a single center, open label, pragmatic, non-inferiority, cluster randomized controlled trial. Patients with a PPL requiring navigational bronchoscopic sampling will be included. We have one EMN platform and one SSCB platform at VUMC. The platform set up in each of our two operating rooms will be randomly allocated each morning. Any navigational bronchoscopy scheduled in a given operating room that day will be performed with the platform allocated to that room on that day.

Study Population

Inclusion Criteria:

1. ≥ 18 years of age at time of bronchoscopy.
2. Undergoing navigational bronchoscopy for biopsy of PPL

Exclusion Criteria

1. Enrolled in a different study requiring use of one specific platform
2. Subject declines to participate

Endpoints

Primary Outcome

The primary endpoint will be diagnostic yield, defined as the proportion of procedures that results in acquisition of lesional tissue.

Lesional tissue is defined by the presence of pathological findings that readily explain the presence of a pulmonary lesion. The following common pathological findings are pre-specified:

- Malignancy
- Specific benign pathologic finding including
    - Organizing pneumonia
    - Frank purulence/robust neutrophilic inflammation
    - Granulomatous inflammation
    - Other specific benign findings such as hamartoma, amyloidoma or other uncommon causes of PPLs with distinctive pathological patterns.

Biopsies not meeting any of the above lesional pathological criteria will be adjudicated as not meeting the primary outcome (not being “diagnostic"), including biopsies with normal lung parenchyma or airway components on biopsy, atypia not diagnostic of malignancy, or non-specific inflammation. A blinded panel will review all non-malignant biopsies at the end of accrual to confirm specific benign or non-diagnostic findings on biopsy. Procedures will be adjudicated as not meeting the primary outcome if the procedure starts but biopsies are not obtained (due to failure to navigate to the lesion, or complication, or equipment failure). A procedure will be considered started at induction of general anesthesia.

Biopsies obtained without the use of EMN or SSCB (e.g., sampling of central lymph nodes using the linear endobronchial ultrasound bronchoscope) will not be included in the diagnostic yield calculations. In case of repeat bronchoscopies, only the index bronchoscopy will be included in the diagnostic yield calculation.

Secondary outcomes

1. Duration of procedure (in minutes), defined as time from the start of airway registration to the removal of the bronchoscope after completion of navigation procedures.

Exploratory outcomes

1. Need for additional diagnostic procedures directed at the PPL of interest
2. Radiation exposure
3. Diagnostic accuracy at 12-months post-biopsy

Safety outcome

1. Rate of procedure complications including respiratory failure, pneumothorax, anesthetic complications, and bronchopulmonary hemorrhage

Outcomes Definitions

- *Rate of complications:* Number of procedures resulting in any complication divided by the total number of procedures.
- *Rate of specific complication:* Number of procedures resulting in a specific complication divided by the total number of procedures.
- *Need for additional diagnostic procedures:* Any diagnostic procedure performed after the study bronchoscopy which targets the same peripheral lesion (including repeat bronchoscopy, transthoracic needle biopsy, or surgical lung biopsy) will be considered an additional diagnostic procedure. Repeat biopsies of lesions determined to be malignant by study bronchoscopy which are 1) performed specifically to obtain additional tissue for further testing but that does not change the malignant diagnosis, or 2) therapeutic surgical resection of such lesions, will not be considered additional diagnostic procedures.
- *Radiation exposure:* Radiation dose delivered to the patient during the study bronchoscopy, recorded as a dose area product (mGy/cm2).
- *Diagnostic accuracy:* Number of true positive (malignant) lesions plus true negative (specific benign diagnosis) lesions with no evidence of malignancy at 12-month follow-up (no interval biopsy diagnostic of malignancy, regression on CT or stable size with no plan for repeat diagnostic procedure), divided by the total number of biopsied lesions.

Randomization and Blinding

All patients meeting the eligibility criteria for this study will be enrolled. Cluster randomization will be used for this study given impracticability of patient-level 1:1 parallel randomization (see Informed Consent section for details). The EMN and SSCB platforms will be

randomly allocated to our two operating rooms each day. All patients undergoing a navigational bronchoscopy will have their procedure performed with the platform assigned to their operating room (OR) for the day. A biostatistician not involved in patient care will generate the randomization sequence. Random permuted blocks may be used to ensure balanced cluster allocation. A bronchoscopy scheduler with no knowledge of the allocation scheme will schedule each patient into one of the two operating rooms. Allocations will be concealed in sealed envelopes which will be opened every morning by the OR staff preparing the rooms.

It is not possible to blind the bronchoscopist or the patient to the platform used for each procedure, as they are both large distinctive-appearing pieces of equipment. However, thoracic pathologists and bronchoscopy schedulers will remain blinded, such that allocations should be unable to influence their histopathological interpretation or scheduling of procedures in a given OR, respectively.

Study Procedures

Written research informed consent for the collection of data will be integrated within the clinical workflow when obtaining procedural consent (refer to Informed Consent section below) and all eligible patients will be enrolled. An allocation envelope will be opened by OR staff each morning to determine which room each platform will be set up in. The pre-operative steps and procedure will proceed per usual standard of care. Intubation and ventilation will follow our standard clinical protocol which is identical for both platforms (8.5 mm size endotracheal tube, a recruitment maneuver once the endotracheal tube is secured (PEEP of 40 cmH20 for 40 seconds), followed by ventilation with a PEEP of 15 cmH20 with as minimal FiO2 needed to maintain a SpO2 of >90%). The navigation procedures will be planned using pre-procedure CT scans of the chest and the planning software specific to each platform.

Bronchoscopy will be performed by interventional pulmonologists with expertise in navigational bronchoscopy and as per standard of care. Procedures will be performed under general anesthesia with neuromuscular blockade. Radial endobronchial ultrasound will be available for all procedures. Biopsies will be obtained using transbronchial needles, biopsy forceps, cytology brushes, cryoprobes, and/or other sampling devices at the discretion of the

bronchoscopist. Rapid on-site evaluation will be performed to assess for specimen adequacy. Additional biopsies obtained without the use of guided bronchoscopy (e.g., sampling of central lymph nodes using the linear endobronchial ultrasound bronchoscope) will be collected if clinically indicated but will be excluded from PPL diagnostic yield calculations. The procedure will be deemed non-diagnostic if the proceduralist is unable to reach the nodule (no biopsies obtained, representing navigation failure) or if a complication occurs before biopsies are obtained. All patients will recover based on our usual standard of care, which includes two hours of monitoring in the PACU before being discharged.

Patients not diagnosed with malignancy following bronchoscopic biopsy will be followed clinically per standard of care. We will review their interval chest CT scans to assess the target lesion for progression, regression, or stability for up to 12 months. If any additional biopsies of the target lesion are obtained by alternative means (transthoracic needle biopsy, surgical biopsy), definitive pathological results as previously defined will be compared to the bronchoscopy biopsies.

Study Calendar

Study Procedures	Day 1	Within 7 Days	3 Month	6 Months	12 Months
Inclusion/exclusion criteria	X				
Randomization	X				
Clinical and demographic data	X				
Adverse events	X	X			
Pathology review		X			
Chest CT	Per SOC		Per SOC	Per SOC	Per SOC
Bronchoscopy	Per SOC				
Follow-up			Per SOC	Per SOC	Per SOC

Assessment of Resource(s)

The Interventional Pulmonology group at Vanderbilt University Medical Center performs approximately 400 navigational bronchoscopies per year and is one of the leading centers in navigational bronchoscopy in the US, both from a volume and expertise standpoint. The group generally consists of three full time board-certified interventional pulmonologists, an

interventional pulmonology fellow, a dedicated interventional pulmonology nurse practitioner, and a dedicated group of outpatient personnel (nurses, nurse navigators, and dedicated schedulers). Obtained samples are analyzed per standard of care by a group of thoracic pathologists. Anesthesia for the procedures will be provided by general and cardiothoracic anesthesiologists supervising CRNAs with specific expertise in bronchoscopy anesthesia.

RECRUITMENT AND ENROLLMENT PROCEDURES

The vast majority of navigational bronchoscopy procedures at VUMC meet eligibility criteria for this study, with very few procedures annually being performed in pediatric patients or for alternative studies requiring a specific navigational platform. After confirming the patient meets the eligibility criteria, the patient will be approached for enrollment in the study. Written research informed consent for the collection of data will be integrated within the clinical workflow when obtaining procedural consent as described below.

STATISTICAL CONSIDERATIONS

Sample Size Calculation

EMN diagnostic yield varies widely in the literature (1). Based on data from prior studies and our own published data, we estimated the diagnostic yield of EMN to be 80% (10, 12). The diagnostic yield of SSCB has not been fully elucidated, but published data suggest an overall diagnostic yield of 80% as well (5,7). Assuming the diagnostic yield for EMN is 80%, with a non-inferiority margin set at 10%, cluster size of 2, and no intracluster correlation, we need 202 clusters (OR-days) to have an 80% power to conclude noninferiority at a one-sided type I error rate of 5%, which corresponds to a target of 425 subjects to reach 202 per arm. The noninferiority margin has been chosen based on what would be considered a clinically significant difference (or, put differently, a difference which might influence a hospital to purchase one platform over the other). In case our average cluster size does not reach 2, we will plan to increase the number of clusters to meet our target enrollment of 425 subjects to reach 202 per arm.

Non-Inferiority Tests for the Difference of Two Proportions in a Cluster-Randomized Design

Test Statistic: Likelihood Score Test (Farrington & Manning)

Hypotheses: H0: P1 - P2 ≤ D0 vs. H1: P1 - P2 > D0

Power	Group 1 Clusters/ Items K1/M1	Group 2 Clusters/ Items K2/M2	Group 2 Prop P2	Group 1 Non-Inf. Prop P1.0	Group 1 Actual Prop P1.1	Non-Inf. Diff D0	Actual Diff D1	Intra-Cluster Corr. ICC	Alpha
0.80275	2/128	2/128	0.8000	0.7000	0.8000	-0.1000	0.0000	0.0000	0.025
0.80327	2/101	2/101	0.8000	0.7000	0.8000	-0.1000	0.0000	0.0000	0.050

Interim Analysis

There is no plan for interim analysis and thus no boundaries for early stopping.

Statistical Analysis Plan

Standard consort diagram will be created. Descriptive statistics including means, standard deviations, and median and interquartile ranges for continuous parameters, as well as percentages and frequencies for categorical parameters will be presented. To adjust for intracluster correlation, a generalized linear mixed model with binary outcome will be used to compare the primary outcome (diagnostic yield) between the comparator groups. Additional comparisons between groups will be made using either generalized linear mixed model or linear mixed model.

Subgroup analysis will be performed for the following subgroups

- Nodule size: <1.5cm, 1.5-3cm, >3cm
- Presence of bronchus sign
- Solid vs subsolid nodule
- Peripheral vs central location – *Peripheral defined as outer 1/3 of chest*

DATA COLLECTION

All data collected is captured as part of routine clinical care and will be supplemented with abstraction from EPIC as needed. Data will be collected in a Health Insurance Portability and Accountability Act compliant REDCap database. REDCap (Research Electronic Data Capture) is a secure, web-based application that is flexible enough to be used for a variety of types of research. REDCap provides an intuitive user interface that streamlines project

development and improves data entry through real-time validation rules (with automated data type and range checks).

REDCap also provides easy data manipulation (with audit trails for reporting, monitoring and querying patient records) and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). In addition to traditional data capture functionality, REDCap's survey capabilities are a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. All data collection projects rely on a thorough, study-specific data dictionary, defined by all members of the research team in an iterative, self-documenting process. This iterative development and testing process results in a well-planned and individualized data collection strategy.

REDCap servers are housed in a local data center at Vanderbilt, and all web-based information transmission is encrypted (10). REDCap was developed specifically around HIPAA-Security guidelines and is recommended to Vanderbilt researchers by both our Privacy Office and Institutional Review Board. REDCap has been disseminated for local use at more than 2,700 other academic/non-profit consortium partners in 117 countries. Vanderbilt leads the REDCap Consortium, which currently supports more than 490,000 projects and 654,000 users.

Data capture may be facilitated by the use of the REDCap Clinical Data Interoperability Services (CDIS) tools. Project team members listed as Key Study Personnel with existing electronic health record (EHR) system access rights will make use of REDCap CDIS tools. These tools are designed to enable transfer of relevant study-related data from the Vanderbilt Research Derivative and/or directly from the EHR into REDCap.

The Research Derivative is a database of clinical and related data derived from the Vanderbilt University Medical Center's (VUMC) clinical systems and restructured for research. Data is repurposed from VUMC's enterprise data warehouse, which includes data from StarPanel, VPIMS, and ORMIS (Operating Room Management Information System), EPIC, Medipac, and HEO among others. The medical record number and other person identifiers are

preserved within the database. Data types include reimbursement codes, clinical notes and documentation, nursing records, medication data, laboratory data, encounter and visit data, among others. Output may include structured data points, such as ICD 9 or 10 codes and encounter dates, semi-structured data such as laboratory tests and results, or unstructured data such as physician progress reports. The database is maintained by the Office of Research Informatics under the direction of Paul Harris, Ph.D.

DATA AND SAFETY MONITORING BOARD (DSMB)

The principal role of the DSMB is to assure the safety of patients in the trial. They will regularly monitor safety data from this trial, review and assess the performance of its operations, and make recommendations to the study team and the LHS Platform with respect to:

- Participant safety and risk/benefit ratio of study procedures and interventions

- Protocol amendments (with specific attention to study population, intervention, and study procedures)

- Adherence to the protocol requirements

- Possible early termination of the trial because of new external information, early attainment of study objectives, safety concerns, or inadequate performance

The DSMB will be asked to evaluate any SAEs or unanticipated AEs. Outcomes data may be presented to the DSMB at the DSMB's request with no plan for interim analyses. The DSMB will consist of members with expertise appropriate to the conduct of the study, such as pulmonary medicine, biostatistics, and clinical trials. Appointment of all members is contingent upon the absence of any conflicts of interest. All the members of the DSMB are voting members. The Principal Investigator and unblinded study biostatistician will be responsible for the preparation of all DSMB and adverse event reports. The DSMB will develop a charter and review the protocol during its first meeting. Subsequent DSMB meetings will be scheduled in accordance with the DSMB Charter with the assistance of the Principal Investigator. The DSMB will have the ability to recommend that the trial end, be modified, or continued unchanged.

RISKS AND SAFETY REPORTING OF ADVERSE EVENTS

We believe this pragmatic randomized controlled trial to be of minimal-risk given: 1) both systems are standard of care and used interchangeably for this indication; 2) both systems have comparable side effect profile, a prerequisite of the 510(k) FDA clearance of SSCB, since then backed up by additional non-randomized studies of SSCB; 3) in our current practice, it is already arbitrary whether a given patient's procedure will be performed by EMN or SSCB – all of which demonstrate equipoise between groups. Information on adverse events, whether serious or not, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed, and reported as described in the following sections.

Reporting Period

Procedural related risks are described in detail below. For example, adverse events such as pneumothorax and bronchopulmonary hemorrhage may result in the need for a chest tube or blood transfusion, respectively. These clinical adverse events are recorded within the case report form (CRF) and are known potential complications of the usual care procedures. As such, these events will not be reported to the IRB as an adverse event related to the research and instead will be collected as events for the purposes of the DSMB. All serious unanticipated adverse events will be reported to the DSMB and IRB per current institutional standards. These may include events resulting in escalation of care such as the need to remain in the hospital following the bronchoscopy procedure. As these procedures are standard of care for sampling PPLs, collection of data regarding adverse events and serious adverse events will be limited in this study:

- Any serious or non-serious adverse event related to research procedures (i.e., the consent process, HIPAA compliance, etc.) will be collected.
- Any serious adverse event that occurs ≤ 7 days after the procedure.
- A written report will be sent to the DSMB and IRB within 15 calendar days of the PI being notified.

Procedure Related Risks

The procedures being studied are considered standard of care and are being undertaken for routine care of the patient. As such, we do not expect that enrollment in this study will result in an increased risk for the patient above what they are experiencing as part of their routine care. The

risks of navigational bronchoscopy for the biopsy of PPLs are well defined, and include pneumothorax, bronchopulmonary hemorrhage, which could result in the need for a blood transfusion, respiratory failure, and anesthetic complications. Risk of death is estimated around 1/10,000. Pneumothorax is the most common complication, occurring in approximately 2% of cases in a large prospective multicenter study (3) and may result in the need for a chest tube. Existing data for SSCB indicates a similar risk profile, which also underlie its recent FDA clearance via 510(k) pathway which requires a demonstration of similar risk to a predicate approved or cleared device. Procedural risks are collected in the CRF and may be reviewed by the DSMB. As these are considered procedural risks and not research related risks, they will not be reported to the IRB.

Research Only Risks

Key additional risks for study participants are data protection and non-adherence to research consent for the collection of data. All patient related information in this study will be entered and stored at Vanderbilt University Medical Center REDCap database, which requires two factor authentications if accessed from outside of VUMC's firewall. In addition, the research paper consent will be kept in a research binder in a locked file cabinet in a locked office. Only relevant key study personnel will have access to this database and binder as necessary to conduct the research. 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 applicable laws and regulations. All records and data related to the study will be maintained in secure protected spaces, with access restricted to key study personnel approved by the IRB who (i) need access to the information to fulfill the terms and obligations under the Protocol and (ii) are under the same obligations as study personnel to keep the information confidential.

REGULATORY CONSIDERATIONS

Informed Consent

We propose a pragmatic, open-label, cluster-randomized trial to compare the diagnostic yield of these standard of care bronchoscopic platforms (EMN vs. SSCB). We will randomly allocate which system (EMN or SSCB) is set-up in each operating room on a given day, and all

peripheral pulmonary lesion biopsies occurring in that room on that day will be performed with the assigned system.

We currently perform advanced diagnostic bronchoscopy in two operating rooms within the main VUMC ORs. We have one EMN system and one SSCB system. Both systems require time to set up, including moving equipment into and out the OR and running calibration steps. OR staff typically arrives one hour before procedures are scheduled to begin each day to set up. Each OR hosts 5-8 bronchoscopies daily, up to four of which on a given day may be EMN/SSCB cases (often back-to-back with each other). Additionally, these procedures need to be planned by the bronchoscopist ahead of time. To accommodate traditional individual patient-level randomization would require moving these platforms between ORs multiple times daily and planning the procedure after consent and enrollment. This would result in a tremendous disruption of our workflow, procedural delay, and suboptimal patient care rendering this study impracticable. Furthermore, about 20% of navigational bronchoscopy cases are performed only after intrathoracic lymph nodes are sampled and negative for malignancy (per rapid on-site cytological examination). Patients with evidence of cancer in their lymph nodes would no longer have an indication for navigational bronchoscopy and would then be excluded after randomization if we were to use traditional individual patient-level randomization, which would significantly impact accrual and power.

Scheduling the EMN and SSCB systems into each room in advance to allow patients to be scheduled into these rooms based on their randomized allocation appears superficially feasible but would result in procedures being delayed days to weeks potentially, as we do not always have multiple slots available for peripheral pulmonary lesion biopsy on a given day, which is not acceptable from a clinical perspective. Furthermore, we meet a large proportion of our patients the day of the procedure, thus would be unable to enroll and randomize before the day of procedure. When patients are consented for the diagnostic bronchoscopy procedure, eligible patients will then be consented for inclusion in this trial and collection of their data.

Common etiologies of peripheral pulmonary lesions include malignancy and infections, which makes nearly all of these procedures clinically urgent.

These logistical issues have two notable practical consequences:

1. Given the set-up time required for these bronchoscopic platforms, they cannot be moved between rooms once set up for the day.
2. From the perspective of an individual patient planned to undergo bronchoscopic biopsy of a peripheral pulmonary lesion, it is currently arbitrary whether their biopsy will be performed with EMN or SSCB, which depends on the day they happen to be scheduled and which of our two platforms (EMN and SSCB) happen to be set up in the OR that day. Given no comparative data exists between these two modalities, we have no clinical reason to select patients into one system versus the other. However, the provider retains autonomy to determine the most appropriate course of clinical care based on the presentation of the patient. If new information on treatment practices were to arise and one of our two platforms were recommended for specific cases, the corresponding patients would receive the appropriate treatment and would not be eligible for this study.

In the context of these issues, we believe the only feasible study design for this trial is cluster randomization as previously described. The only additional risks of participation in this study beyond SOC are confidentiality and non-adherence to research consent. All data will be maintained in a secured REDCap database by proceduralists who have already been exposed to the patient's PHI while providing clinical care. The clinical team has a REDCap database in which it is collecting data on these procedures for QI projects and QI analysis. This study will extract these data from the QI systems; no new data are being collected. Research informed consent will be obtained when clinical informed consent is obtained for the procedure. Research informed consent will be scanned, by a study coordinator, into the secured REDCap database and the research paper consent will be kept in a research binder in a locked file cabinet in a locked office. Only the study team will have access to the locked file cabinet. In addition, a note will be written in the patient's electronic medical record stating that the patient was enrolled in this study.

Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) and Data and Safety Monitory Board (DSMB) per current institutional standards. The trial will not be initiated until there is approval by the IRB of the protocol. The IRB should be duly constituted according to regulatory requirements. The investigator will inform the IRB of the progress of the trial at least yearly. Any changes to the protocol will be made in the form of a written amendment and must be approved by the IRB prior to implementation. Protocol changes to eliminate an immediate hazard to a trial patient may be implemented by the investigator immediately. The investigator must then immediately inform the IRB and DSMB.

Good Clinical Practice

This study will be carried out in compliance with the protocol and Good Clinical Practice (GCP), as described within:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described within the above and thereby to adhere to the principles of Good Clinical Practice with which the above conform.

Confidentiality

It is the responsibility of the investigator to ensure the confidentiality of patients participating in the trial. Case report forms (CRFs) and other documents submitted to regulatory authorities must not contain the name of a trial patient. All patients in the trial will be identified by a unique identifier which will be used on all CRFs, and any other material submitted to regulatory authorities. All case report forms, and any identifying information must be kept in a secure location with access limited to the study staff directly assisting with the trial.

Study Termination

Reasons for study termination may include, but are not limited to, the following:

1. Investigator non-compliance with the protocol, GCP or regulatory requirements
2. Insufficient enrollment
3. Safety concerns
4. Decision by suppliers to modify or discontinue the availability, development or manufacture of protocol-indicated treatment or device
5. A request to discontinue the study by the IRB or a recognized regulatory authority

Benefits, Compensation and Additional Costs

There will be no financial compensation for participation. There is no additional benefit to the patient by participating the in the trial. Data from this study will be beneficial to the field. There will be no additional cost to subjects for participating in this study. Subjects and/or their insurance companies will be responsible for all care provided as part of the procedure as this service is part of the standard of care they would receive for their condition.

STUDY COORDINATION

Trial Compliance

This is an investigator-initiated study. The Principal Investigator, Fabien Maldonado, M.D. is conducting the study and Vanderbilt University Medical Center (VUMC) will act as the sponsor.

Protocol Deviations

Vanderbilt University Medical Center is responsible for implementing and maintaining quality assurance and quality control to ensure that studies are conducted according to the protocol, GCP, and all applicable regulatory requirements. A protocol deviation is any noncompliance with the protocol. Noncompliance can be on the part of the study participant, the investigator, or the study site staff. Deviations to the protocol are not permitted except when necessary to eliminate an immediate hazard to study subjects.

Record Retention

An electronic case report form (eCRF) is required and must be completed for each included participant. Records will be retained compliant with institutional, federal, and local regulations. Secondary use of the data will be with IRB approval. The dataset may be made available outside of the study team on reasonable request with approval from an authorized Institutional Review Board and concurrence with the study team that the data are fit for purpose.

PLANS FOR DISSEMINATION OF FINDINGS

Any manuscript or releases resulting from the collaborative research must be approved by the investigator and will be circulated to applicable participating investigators prior to submission for publication or presentation. A publication plan consistent with the international Committee of Medical Journal Editors (ICMJE) will be created prior to analysis and publication of any data. All data will be made available to authors as required. The publication of sub-studies and post-hoc analyses will not precede the primary publication. Publication of results will be determined by the investigators. All authors are expected to disclose financial or affiliations that could be considered conflicts of interest per journal or medical society requirements.

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