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VERITAS

THO 19102: NaVigation Endoscopy to Reach Indeterminate lung nodules versus Transthoracic needle Aspiration, a randomized controlled Study (VERITAS)

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PROTOCOL SYNOPSIS

Title	Na**V**igation **E**ndoscopy to **R**each **I**ndeterminate lung nodules versus **T**ransthoracic needle **A**spiration, a randomized controlled **S**tudy
Short title	VERITAS
Study objective	In this study, we propose to study in a 1:1 randomized controlled trial the diagnostic accuracy of navigation bronchoscopy pathway with fluoroscopic navigation (F-Nav) using a non-inferiority study design (primary endpoint) versus the current clinical standard of care: CT-guided biopsy.
Study device	SuperDimension and Fluoroscopic navigation.
Design	Multicenter, randomized, non-inferiority study.
Study centers	Vanderbilt University Medical Center, and approximately 5 to 7 additional sites based in the United States.
Number of subjects	N=258
Subject follow-up	Patients with non-diagnostic biopsy or benign diagnoses will be followed for up to one year as part of the study with further diagnostic procedures as clinically required.
Inclusion criteria	1. ≥ 18 years of age at time of signing informed consent. 2. Referred for biopsy of a single indeterminate pulmonary nodule, with the following characteristics regarding size, location, accessibility, and probability of malignancy: a) Intermediate or high pre-test probability of malignancy as defined by a pre-test probability of malignancy between 10% and 100%, using a validated clinical prediction model, which is either: i. The Brock model if no PET scan data are available, or ii. The Herder model if PET-CT data are available. b) Size between 10 and 30 mm (long diameter). c) Location peripheral, here defined as occupying the middle or outer third lung zones. d) Accessible via navigation bronchoscopy and also accessible via CT-guided biopsy (i.e. the nodule is clinically suited to equal access by either procedure), as confirmed by an independent interventional panel (see Section 4.5).
Exclusion criteria	1. Patients with proximal nodules, as defined by nodules accessible via conventional bronchoscopy (endobronchial lesions) or linear endobronchial ultrasound will not be eligible for the study (as these patients would standardly undergo bronchoscopy already). 2. Patients with multiple nodules requiring biopsy (patients may have other nodules not considered for biopsy). 3. Radiologically abnormal mediastinal or hilar lymph nodes requiring endobronchial ultrasound. 4. Patients for whom stereotactic body radiation therapy is planned even if biopsies show no evidence of malignancy. 5. Patients with contraindication to biopsy or deep sedation/general anesthesia. 6. Patients unable or unwilling to comply with study follow-up schedule. 7. Patients previously randomized to the study. 8. Patients unable to provide documented informed consent. 9. Patients who are pregnant or nursing.

Primary endpoint	The primary endpoint will be diagnostic accuracy, as defined by the rate of technically successful biopsies leading to a definitive diagnosis, comparing the bronchoscopy pathway (navigation bronchoscopy) to the CT-guided biopsy pathway. Definitive diagnoses are pre-defined as any of the following:
	• Malignancy on histology, **OR**
	• Biopsies with abnormal tissue (excluding normal or absence of lung parenchyma) that are followed by a surgical lung biopsy yielding the same histological diagnosis, **OR**
	• Specific benign histopathologic finding which accounts for the presence of a lung nodule (specifically including organizing pneumonia, frank purulence, granulomatous inflammation, or other specific benign finding) **AND**
	• Absence of malignancy (true negative) through 1-year longitudinal CT follow-up, defined as:
	  ○ The nodule markedly regresses or resolves on follow-up imaging, **OR**
	  ○ a persistent nodule has not been diagnosed as malignant, **AND**
	  ○ there are no plans for repeat invasive diagnostic procedures through 12 months follow-up.
	
	Biopsies with normal or absence of lung parenchyma, atypia and non-specific inflammation will be considered non-diagnostic. All biopsies not diagnostic of malignancy (from both arms) will be centrally reviewed by an independent expert lung pathologist blinded to the biopsy technique, and follow-up diagnosis will be established during routine clinical follow-up after 1 year.

Secondary endpoints	• Rate of pneumothorax. • Rate of pneumothorax requiring chest tube placement. • Clinically significant bleeding (defined by bleeding requiring intervention). • Need for hospitalization after procedure. • Duration of the procedure. • Procedural factors associated with improved yield (type of biopsy, number of biopsies, use of radial ultrasound, presence of a bronchus sign, biopsy site). • Need for additional nodule biopsy. • Need for additional procedure for staging. • Radiation exposure from fluoroscopy-guided bronchoscopy and CT for CT-guided biopsy. • Need for F-Nav during navigation bronchoscopy. • Diagnostic yield, defined as the rate at which histopathology is obtained which explains the presence of a nodule (according to definitions set forth for the primary endpoint) and permits post-biopsy clinical decision-making without need for immediate additional diagnostic procedures. • Rate at which the biopsy procedure yields a confident clinical diagnosis (including any added yield from endobronchial ultrasound-guided mediastinal and/or hilar lymph node biopsies or microbiologic studies which yield an explanation for a nodule despite non-diagnostic biopsy specimens).

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Statistical methodology	The primary analysis will use a Bayesian approach, the initial power analysis uses a Frequentist approach. We assume that diagnostic accuracy for CT-guided biopsy is 90%. The non-inferiority margin is set at 10 percentage points, and one-sided type I error rate is set at 5%. Thus, if the true diagnostic accuracy for navigation bronchoscopy is lower than 80%, we will have 5% probability (type I error rate) to incorrectly conclude noninferiority.
Interim analysis	No interim analyses are planned for this trial.

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1. General Study Information

Principal Investigators: Fabien Maldonado, MD and Najib Rahman, DPhil MSc FRCP

Statistician: Tatsuki Koyama, PhD

Advisor: Pierre Massion, MD

Title: Na**v**igation **e**ndoscopy to **r**each **i**ndeterminate lung nodules versus **t**ransthoracic needle **a**spiration, a randomized controlled **s**tudy (VERITAS)

2. 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. Participating study sites shall only allow individuals who are appropriately trained and qualified to assist in the conduct of the study.

3. Purpose of the study

3.1 Hypothesis

Lung cancer accounts for more cancer-related deaths in the US than colon, prostate and breast cancer combined, representing approximately 160,000 deaths every year.[1] In 2011, the National Lung Screening Trial (NLST) demonstrated a 20% relative reduction in lung cancer mortality with annual low-dose computed tomography (LDCT).[2] These encouraging results, which were recently confirmed in a large European randomized controlled trial on lung cancer screening, the NELSON trial, have led to the widespread endorsement of lung cancer screening, but implementation is hampered by the high rate of false-positive LDCT studies.[3] An estimated 1.5 million new indeterminate lung nodules are identified every year on chest computed tomography (CT) in the US, translating to around 4,000 nodules per day in the US alone, and implementation of LDCT-based lung cancer screening is estimated to increase these numbers substantially, as more than 10 million US adults are candidates for screening based on accepted eligibility criteria.[4] In the NLST, approximately 40% of individuals randomized to LDCT screening had one or more nodules identified during the study period, the vast majority of

which were ultimately proven benign.[2] This means that the diagnosis and management of pulmonary nodules will be an enormous and increasing healthcare need of the future.

The diagnostic algorithm for indeterminate pulmonary nodules is based on pre-test probability of malignancy as determined by validated clinical prediction scores or clinician estimates. Low-probability (<10% chance of malignancy) are followed radiologically with serial CT, while high pre-test probability nodules (>70% chance of malignancy) are typically surgically resected, although tissue confirmation is often necessary even for these nodules.[5] A non-surgical biopsy is typically recommended for nodules with low to intermediate probability of malignancy. High pre-test probability nodules are also frequently biopsied, when surgery is considered higher-risk or when stereotactic body radiation therapy is considered. Options include CT-guided transthoracic needle biopsy or bronchoscopic biopsy. CT-guided biopsy is associated with a general yield estimated at 90%, although studies focusing on nodules < 1.5 cm have reported yields between 70% and 80%.[6-8]There has not been randomized controlled studies comparing CT-guided biopsy to other approaches. The technique is associated with substantial complications: in a population-based study, the rate of pneumothorax was 15% with need for chest tube management in 7%, and the risk of hemorrhage was 1%.[9] Conversely, bronchoscopic biopsy is safer with reported 1.6% pneumothorax, with a need for chest tube management in 0.7%, and a 0.5% hemorrhage risks, but best estimates of yield using conventional navigation techniques approach 75%, with rates below 50% in registry data.[10-12]

One of the main limitations of navigation bronchoscopy is the inability to confirm successful navigation, as the roadmap planning to the nodule is based on preoperative CT images obtained at lung volumes substantially different than those achieved during deep sedation or general anesthesia required during bronchoscopy. The recently introduced FDA-approved enhanced fluoroscopy imaging device, F-Nav (SuperDimension, Medtronic, Minneapolis, Minnesota, USA), allows visualization of fluoroscopically-invisible nodules, re-registration and adjustment of the target. Using this more "real time" technique, the diagnostic yield approaches 85% in retrospective data from Vanderbilt University Medical center, Nashville, TN. In addition, endobronchial ultrasound biopsies of mediastinal lymph nodes are diagnostic in 13% of patient without CT or PET scan abnormalities, which emphasizes the importance of bronchoscopy.[13] If these promising results were confirmed, the widespread adoption of F-Nav would allow diagnostic resolution of indeterminate pulmonary nodules with the following advantages over CT-guided biopsy: (1) avoidance of potentially life-threatening complications associated with CT-guided biopsies, (2) performance of complete mediastinal staging via endobronchial ultrasound when malignancy is confirmed, in a single procedure under a single sedation / anesthetic session and (3) potential biopsy of multiple indeterminate lung nodules in the same procedure. This has the potential to significantly decrease mortality, morbidity and healthcare costs, and if proven, to be a robust diagnostic methodology, to become the standard of care for thousands of patients per year.

3.2 Aims *and* Objectives

In this study, we propose to study in a 1:1 randomized controlled trial the diagnostic accuracy of navigation bronchoscopy (NB) with F-Nav (SuperDimension iLogic 7.2 ENB platform and later (SuperDimension, Medtronic, Minneapolis, Minnesota, USA)) using **a non-inferiority study design (primary endpoint) versus the current clinical standard of care: CT-guided biopsy.** We will in addition compare: complications rate including rate of pneumothorax and clinically significant bleeding, need for hospitalization

after procedure, time to procedure, duration of the procedure, need for additional nodule biopsy, need for additional procedure for staging, radiation exposure from fluoroscopy and CT, and need for F-Nav during navigation bronchoscopy (secondary endpoints). Follow up has been chosen to be pragmatically deliverable while allowing full assessment of key outcomes, including false negatives to provide a robust, clinically meaningful trial result.

4. Study Design

4.1 General Study Design

This is a randomized 1:1 non-inferiority trial of the new diagnostic algorithm versus the current standard of care. A non-inferiority design has been chosen to reflect the clinically most important outcome (diagnostic accuracy) in the presence of a technology which is likely to reduce significant current complications / adverse events, and allow in the same procedure mediastinal staging and, potentially, additional bronchoscopic interventions (such as airway inspection, biopsy of additional nodules).

4.2 Patient Inclusion and Exclusion Criteria

Inclusion criteria:

1. Patient is ≥ 18 years of age at time of signing informed consent .

2. Patient is referred for biopsy of a single indeterminate pulmonary nodule, with the following characteristics regarding size, location, accessibility, and probability of malignancy:

    a) Intermediate or high pre-test probability of malignancy as defined by a pre-test probability of malignancy between 10% and 100%, using a validated clinical prediction model, which is either:

        i. The Brock model[14] if no PET scan data are available, or
        ii. The Herder model[15] if PET-CT data are available.

    b) Size between 10 and 30 mm (long diameter).

    c) Location peripheral, here defined as occupying the middle or outer third lung zones.

    d) Accessible via navigation bronchoscopy and also accessible via CT-guided biopsy (i.e. the nodule is clinically suited to equal access by either procedure), as confirmed by an independent interventional panel (see Section 4.5).

        Note: Prior to randomization, the main purpose of this study-provided central review is to establish panel agreement with local expertise offered by the participating study site, that local management of a consented candidate patient at the site can be achieved by standard of care navigation

bronchoscopy or equally achieved by standard of care CT-guided biopsy (with either procedure able to be performed at the local institution).

Exclusion criteria:

1. Patients with proximal nodules, as defined by nodules present in the proximal 1/3 of the lung by dedicated software analysis (described below) will not be eligible for the study.
2. Patients with multiple nodules requiring biopsy (patients may have other nodules not considered for biopsy).
3. Radiologically abnormal mediastinal or hilar lymph nodes requiring endobronchial ultrasound.
4. Patients for whom stereotactic body radiation therapy is planned even if biopsies show no evidence of malignancy.
5. Patients with contraindication to biopsy or deep sedation/general anesthesia.
6. Patients unable or unwilling to comply with study follow-up schedule.
7. Patients previously randomized to the study.
8. Patients unable to provide documented informed consent.
9. Patients who are nursing or pregnant as verified by an optional standard of care pregnancy test. (Testing required only if deemed clinically necessary by the patient's study physician.)

4.3 Withdrawal of Patients

The reasons for study exit of all enrolled patients will be documented on the applicable case report form electronic case report form (eCRF). In the event patient withdraws consent during the study, the date of withdrawal will be documented. If the study investigator voluntarily removes a subject from further study participation, supporting documentation must be in place for the rationale and date of removal. Every attempt will be made to contact patients who are non-compliant: subjects will be considered lost to follow-up once the following steps have been taken:

- Two phone calls should be made to the patient. Each attempt should be clearly documented in the source documents and the response or lack thereof should be captured.
- If there is no response to the phone calls, then certified letter should be sent. A copy of the letter will be kept on record.
- After a period of two weeks after the aforementioned interventions, the patient will be considered lost to follow-up. Study exit form will be completed.

4.4 Patient Flow

Potential candidate patients in the standard of care setting will be evaluated by a lung nodule expert at the study site for the presence of a single 10-30mm (longest diameter) indeterminate peripheral lung nodule with a pre-test probability of malignancy between 10% and 100%. Consented patients will subsequently receive additional review by central expert opinion provided by the study, in order to verify the patient's single indeterminate peripheral lung nodule is suitable for both navigation bronchoscopy and CT-guided biopsy.

4.5 Image Transfer and Interventional Panel Adjudication

An independent expert interventional panel composed of an interventional pulmonologist and an interventional radiologist will review the chest CT of screened patients to confirm suitability for navigation bronchoscopy and CT-guided biopsy. Neither expert will be aware of the other's decision. The panel is required to give a view if either of these techniques is technically feasible (and not which is "better"), with the interventional pulmonologist assessing the feasibility of navigation bronchoscopy and the interventional radiologist assessing that of CT-guided biopsy. Each participating institution receives an institution-wide account of the LungCloud™ platform. The LungCloud™ is provided by Neurotargeting LLC, a spin-off of Vanderbilt University. The LungCloud™ is a health IT clinically approved system for the collection of complete data sets in the clinical flow, including but not limited to clinical outcome, radiology notes and scans. The LungCloud™ is set up as a network of accounts that can be interconnected around a clinical study. The managing institution creates a Clinical Trial inside the LungCloud™ and ties it to each of the institutions. Each institution is then able to collect and share data for the clinical study. Data is collected in the clinical flow and from PACS and stays at all time in the LungCloud™ instance of the institution owning the data.

Image data is encrypted and sent to the institution's LungCloud™. Automatic uploading of images is achieved through what is referred to as the LungDrive. This is a process that runs on the end user's machine and works in a way similar to Box or Dropbox, i.e., any new image volume placed in a specific folder is automatically encrypted and uploaded to the account repository. The non-imaging data can be entered into the system and associated with the imaging data through web-based forms customized to the end users. Images are reconstructed in 3D and can be reviewed in any view (sagittal, coronal or axial). The system offers a series of web-based user interfaces that permit inspecting and visualizing both imaging and non-imaging data.

The LungCloud™ allows each site's clinical study coordinator to manage patients that have to be added to the clinical study. Informed consent can be electronically acquired or added manually in the system. After informed consent has been obtained, the patient's de-identified data will be shared with the study primary site.

As part of the study, the subject's chest CT will be displayed in the clinical study review web-portal for analysis by the independent interventional panel consisting of (1) an interventional pulmonologist expert in navigation bronchoscopy and (2) an interventional radiologist expert in CT-guided biopsy. The lung nodule will be assessed for its location in the proximal, middle or outer third of the lung by an independent expert lung nodule physician using a validated software analysis. Nodules accessible by ultrasound guided TTNA, conventional bronchoscopy or linear EBUS will be excluded. Nodules located in the middle or distal third will be included. If

the nodule is deemed amenable to both bronchoscopic and CT-guided biopsy approach, the patient will be randomized.

This assessment involving central review by the interventional panel is intended to occur within **3 business days** after informed consent is obtained. Subsequent randomization of eligible patients is anticipated in conjunction with confirmation of enrollment (as outlined below in Section 5), with initiation of navigation bronchoscopy or CT-guided biopsy to occur within 3 weeks (30 calendar days) after a site is notified of randomization. In the event that a CT scan cannot be uploaded to LungCloud™ expeditiously enough for adjudication to occur within the mandatory 3 day post-informed consent window, central adjudication will proceed using one or multiple representative axial CT slices uploaded to CRF 2 in the study REDCap database.

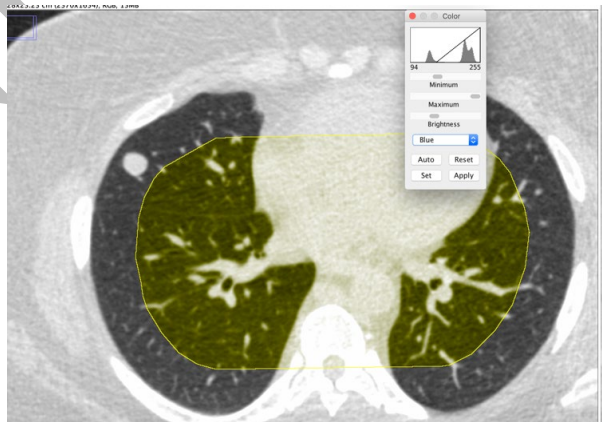
Exclusion criteria for accessibility via navigation bronchoscopy:

1. Nodules with an airway greater/equal to 3 cm away from the lung nodule
2. Nodules located in areas deemed unreachable by an expert interventional bronchoscopist

Exclusion criteria for accessibility via CT-guided biopsy:

1. All nodules for which a fissure would have to be crossed
2. All nodules for which a large bulla would have to be crossed
3. All nodules located in areas deemed unreachable by expert interventional radiologist

To determine if a nodule falls into the outer 1/3, middle 1/3 or proximal 1/3 of the lung parenchyma, proprietary software with be utilized to map zones of the lung as previously described.[16] "CT Pulmo 3D" workflow using OsiriX which automatically analyzes the lung parenchyma and defines the contours of both lungs. If a nodule is within the outer 2/3 of the lung parenchyma or the nodule touches the border of the outer 2/3 of the lung parenchyma the nodule will be considered candidate for study. Each site will be provided with the zone of the nodule (outer, middle or inner 1/3) and an image of the lung zones and nodule prior to the procedure. The figure below depicts an example of lung segmentation and outer 1/3 determination using CT Pulmo 3D.



4.6 Intervention Arm: Bronchoscopy Pathway

The intervention arm will consist of electromagnetic (EMN) navigation bronchoscopy using the Medtronic SuperDimension platform with F-Nav. Patients' available DICOM CT images will be uploaded into the planning software. CTs obtained more than 21 days before the planned procedure, and CT not meeting minimal technical requirements for optimal roadmap planning (adequate CT reconstructions and slice thickness of 1.5mm or less) will be repeated before the procedure. Bronchoscopy will be performed by interventional pulmonologists with expertise in navigation bronchoscopy (as defined by more than 100 procedures performed in the past 2 years, with at least 25 of these performed with F-Nav). Procedures will be performed under general anesthesia with neuromuscular blockade (to facilitate breath holds required for FNAV image acquisition) in a dedicated bronchoscopy suite or operating room. Bronchoscopy will be performed as previously described with confirmation by radial ultrasound.[17] Suggested intraprocedural flow is detailed in the figure in section #14. Radial ultrasound will be used for confirmation only, and not as a navigational tool (i.e. catheters not aligned with the registered target will be considered non-diagnostic). Biopsies will be obtained using a any-gauge needle, with at least 5 passes obtained per nodule. Forceps biopsies, brushings or other biopsy tools will be performed according to the procedure algorithm. Rapid on-site evaluation will be performed to assess for specimen adequacy. All procedures will be followed by fluoroscopy evaluation of the chest to exclude pneumothorax, and, if indicated, ultrasound and/or formal chest radiograph as per standard of care. The procedure will be deemed non-diagnostic if the proceduralist is unable to reach the nodule or if a complication occurs and therefore no biopsy is obtained.

4.7 Comparison: CT-guided Biopsy Pathway

The control arm of the study will consist of CT-guided biopsy, which will be performed by interventional radiologists with expertise in transthoracic needle biopsy and/or fine needle aspiration (as defined by more than 25 procedures performed in the past two years as a department). Procedures will be performed in a dedicated interventional CT scanner with multi-slice capabilities. Patient analgesia with local anesthesia and moderate conscious sedation will be used. Biopsy number, core biopsy vs. fine needle aspiration, use of coaxial needles, and use of rapid on-site cytologic examination will be at the discretion of the proceduralist per local institutional preferences. Procedures will be followed by limited CT scan and/or chest radiograph to exclude pneumothorax if required per local standard of care. The procedure will be deemed non-diagnostic if the proceduralist is unable to reach the nodule or if a complication occurs and therefore no biopsy is obtained.

1. **Patients not eligible for general deep sedation and general anesthesia and therefore not eligible for bronchoscopy, but potentially eligible for CT-guided biopsy, will be excluded from the study but recorded as such in the CONSORT diagram.**

2. **Patients randomized who fail to present for their assigned intervention will be considered screen-failure**

3. **Patients randomized who present for their assigned intervention but do not undergo the procedure for reasons other than for contraindications to the procedure (per institutional policy) will be analyzed as non-diagnostic procedure, and otherwise considered screen-failure. The cause for cancellation will be recorded in the case report form.**

See Procedural Flow Chart (Section 14).

4.8 Outcomes

Primary endpoint

The primary endpoint will be diagnostic accuracy, as defined by the rate of technically successful biopsies leading to a definitive diagnosis, comparing the navigation bronchoscopy to the CT-guided biopsy pathway. Definitive diagnoses are pre-defined as any of the following:

- Malignancy on histological samples, **OR**
- Biopsies with abnormal tissue (excluding normal or absence of lung parenchyma) that are followed by a surgical lung biopsy yielding the same histological diagnosis, **OR**
- Specific benign histopathologic finding which accounts for the presence of a lung nodule (specifically including organizing pneumonia, frank purulence, granulomatous inflammation, or other specific benign finding) **AND**
- Absence of malignancy (true negative) over 1 year of longitudinal CT follow-up, defined as:
    - the nodule markedly regresses or resolves on follow-up imaging, **OR**
    - a persistent nodule has not been diagnosed as malignant, **AND**
    - there are no plans for repeat invasive diagnostic procedures through 12 months follow-up.

Biopsies with normal or absence of lung parenchyma, atypia or mild inflammation will be considered non-diagnostic. All diagnoses (from both arms) will be determined by a blinded, independent, expert lung pathologist (i.e. blind to the biopsy technique) and all non-diagnostic biopsy specimens will be reviewed by an independent expert pathologist.

Linear EBUS for lymph node interrogation and staging will be performed in the same procedure ***after*** the navigation bronchoscopy for staging purposes as per standard of care.

Secondary endpoints

- Rate of pneumothorax
- Rate of pneumothorax requiring chest tube placement
- Clinically significant bleeding (defined by bleeding requiring intervention)
- Need for hospitalization after procedure
- Duration of the procedure (from bronchoscope in to bronchoscope out for the bronchoscopy arm and from first needle in to last needle out for CT-guided biopsy)
- Procedural factors associated with improved yield (type of biopsy, number of biopsies, use of radial ultrasound, presence of a bronchus sign, biopsy site)
- Need for additional nodule biopsy
- Need for additional procedure for staging

- Radiation exposure from fluoroscopy-guided bronchoscopy and CT for CT-guided biopsy
- Need for F-Nav during navigation bronchoscopy
- Adequacy of specimens collected for molecular testing when needed.
- Diagnostic yield, defined as the rate at which histopathology is obtained which explains the presence of a nodule (according to definitions set forth for the primary endpoint) and permits post-biopsy clinical decision-making without need for immediate additional diagnostic procedures.
- Rate at which the biopsy procedure yields a confident clinical diagnosis (including any added yield from endobronchial ultrasound-guided mediastinal and/or hilar lymph node biopsies or microbiologic studies which yield an explanation for a nodule despite non-diagnostic biopsy specimens).

4.9 Centralized Pathology Review (Core Lab Confirmation)

An independent expert lung pathologist will review all non-diagnostic and benign cases. In case of disagreement with the initial pathology review, a third expert lung pathologist will adjudicate the case.

In all cases, management after intervention-biopsy will be as per standard of care, i.e. patients will be managed according to a participating site's conventional clinical guidelines. For example, patients after a negative biopsy may (1) cross-over to another minimally invasive biopsy, (2) be followed with serial chest CTs or (3) undergo surgery. These subsequent procedures will be part of normal patient care and only be regarded as follow-up data for the purpose of this study (i.e. non-randomized bronchoscopies and CT-guided biopsies will not affect the diagnostic yield for the purpose of this study).

Patients will be followed for up to 12 months if serial imaging by chest CT if clinically indicated (non-malignant pathology without resolution on interval imaging), with suggested scanning cadence at 3 months, 6 months, and 12 months.

4.10 Study Flow

See Procedural Flow Chart (Section 14), Screening Flow Chart (Section 15) and Study Assessment Table (Section 16).

5. Enrollment Procedures

The Vanderbilt-Ingram Cancer Center (VICC) Coordinating Center will coordinate enrollment in the study.

Prior to registration, a copy of the IRB approval at the site will be kept on file at the Vanderbilt-Ingram Cancer Center (VICC) Coordinating Center. Eligible participants will be entered on study centrally in OnCore at the VICC Coordinating Center.

All patients MUST be registered with the Vanderbilt-Ingram Cancer Center (VICC) prior to the start of study procedures such as tissue acquisition. Registration can only be conducted during the business hours of 8AM – 5PM Central Time, Monday through Friday.

Enrollment Process:
Potential patients will be screened using the REDCap VERITAS e-Eligibility tool. Eligible patients will be approached by key study personnel either in person or via phone. Patients who agree to participate will provide signed research informed consent. This can be accomplished using a printed paper consent form which is then scanned and uploaded to VERITAS e-Eligibility upon completion, or electronically via the e-consent module embedded within VERITAS e-Eligibility, in which patients may sign research informed consent electronically (either in clinic or after the e-consent form is emailed to them following full informed consent discussion from key study personnel over the phone). Once signed research informed consent has been obtained, a record for the subject is created in the REDCap VERITAS database. Central adjudication are performed within three business days as described in section 4.5, with determinations entered into the VERITAS database. Once central adjudication is complete, the subject's e-eligibility CRF part 2 is completed indicating whether they are eligible for randomization after central adjudication. Eligible patients are then randomized via a randomization module embedded within the VERITAS database.

Note:

Upon satisfactory review of eligibility documents submitted, the Coordinating Center will approve enrollment and issue a subject ID number if one was not issued at screening. Once registration/enrollment confirmation from Coordinating Center is received, proceed with protocol procedures.

Please contact the assigned Study Contact with any questions regarding this process. You can also reach out to your assigned CRA once the study is activated.

The VICC Coordinating Center will assign Subject ID numbers to all patients whose eligibility has been confirmed. Only patients deemed eligible will be registered to the study. Sequence/study ID numbers will not be re-used if a patient screen fails. Following registration, eligible participants should begin the study consistent with the protocol no later than 28 days after registration/enrollment by the VICC Coordinating Center.

Following registration, eligible participants should initiate navigation bronchoscopy or CT-guided biopsy no later than 30 business days after the site is notified of randomization by the VICC Coordinating Center. If a participant does not receive the procedure following randomization within the allowed time period, the patient may be re-consented or participant's registration on the study will be canceled. The Study Contact should be notified of cancellations as soon as possible.

The purpose of this 30 business day scheduling window is to protect subjects from being randomized to a procedure which overly delays their care, when the alternative procedure could be performed substantially sooner and would otherwise have been utilized in clinical practice outside of this trial. For example, if biopsy procedure #1 cannot be performed for 8 weeks due to local factors (equipment failure, perhaps), but biopsy procedure #2 could be performed within two weeks, the 30-day window protects this patient from a potentially harmful delay in a malignant diagnosis by removing them from the trial so they may proceed with procedure #2 on clinical grounds. However, if a situation arises in which a patient must be scheduled outside the 30-day window but 1) the alternative procedure cannot be performed meaningfully sooner and 2) the delay in biopsy is

not expected to impact any eligibility criteria, the patient may remain in the trial (an example in which point #2 might be invoked: a patient with a 29 mm nodule delayed for 3 months, a sufficiently long interval of time in which the nodule may well have grown to exceed 30 mm diameter and therefore no longer be eligible for the trial). This determination must be agreed upon by both the local PI and the central PI (Maldonado) and will be documented in the "notes" field at the end of REDCap CRF #1.

As is generally accepted, standard of care procedures performed prior to consent, but within the protocol defined screening window for each assessment, can be used for study purposes. All research-only procedures must be performed after patient consent.

Subjects who provide informed consent, but are determined to be ineligible prior to initiation of navigation bronchoscopy or CT-guided biopsy will be considered screen failures and the reason for screen failure will be documented. Subjects who fail to present to their assigned procedure after randomization will be considered screen failures as well. Subjects who present to their assigned procedure but do not undergo the procedure for reasons other than safety will be analyzed on an intention-to-treat basis (see above Section 4.7 for details).

6. Methodology

6.1 Statistical methodology

This study will be a randomized controlled trial of navigation bronchoscopy vs. CT-guided biopsy using a non-inferiority study design. The hypothesis of the study is that the diagnostic accuracy of EMN navigation bronchoscopy using the SuperDimension platform with F-Nav performed by interventional pulmonologists is non-inferior to the diagnostic accuracy of CT-guided biopsy performed by interventional radiologists. Eligible patients will be randomized on a 1:1 basis and the randomization will be stratified by the following two criteria within each center to provide balance between treatment arms on these features:

1. Location in the middle or outer third of the lung
2. Pre-test probability of malignancy (50% or less VS 51% or more)

Within each stratum, block sizes of 2 and 4 will be used to enhance blinding.

Though the primary analysis will use a Bayesian approach, the initial power analysis uses a Frequentist approach. We assume that a diagnostic accuracy for CT-guided biopsy is 90%. The non-inferiority margin is set at 10 percentage points, and one-sided type I error rate is set at 5%. Thus, if the true diagnostic accuracy for navigation bronchoscopy is lower than 80%, we will have 5% probability (type I error rate) to incorrectly conclude noninferiority. With this parameter setting a sample size of 112 per group will give approximately 80% power if the true diagnostic accuracies are 90% for both arms. Considering an attrition rate of 15%, the sample size is 129 per group (258 total). Large volume centers could be expected to enroll 50 patients per year, therefore 6 centers are necessary. One year recruitment plus one year follow-up represents 2 years of recruitment time. The noninferiority margin has been chosen based on the known pneumothorax rate of CT

biopsy which is in excess of 10%, and after polling a number of clinicians who are involved in the diagnostic workup of patients with lung nodules, where this margin was considered reasonable.

6.2 Analysis plan

Analytic populations
The analysis set will be the per-protocol (PP) population, which yields more conservative estimates for the noninferiority objective than the intention-to-treat (ITT) population. The ITT analysis will include every randomized subject assigning a treatment failure for those who drops out without the final data. The ITT analysis will be a secondary, sensitivity analysis.

Prior distribution
The probability of successful diagnostic accuracy for each treatment arm will be modeled with a Beta-Binomial distribution. A non-informative prior Beta (1,1) will be used for both treatment arms.

Interim analysis
No interim analysis is planned for this trial. Interim analyses typically assess for futility and efficacy stops regarding the primary outcome part-way through a trial. However, the primary outcome of diagnostic accuracy requires up to 12 months of radiographic follow-up in patients not determined to have malignant nodules by study biopsy. Therefore, an analysis of this outcome halfway through accrual could not be performed until one year after that enrollment midpoint was reached, at which time we expect enrollment to be complete for the entire planned accrual. An interim analysis of the primary endpoint is therefore impracticable. Interim analyses for safety endpoints are often commonly performed in investigations of new devices or novel interventions, but as both study procedures represent long-standing standard of care options for the tissue sampling of lung nodules, complications of these procedures themselves are not considered risks unique to this research. The primary risk to participation in this research involves patient privacy and confidentiality, any breach of which will be reported to the PI and appropriate regulators on an ongoing basis as described later in this protocol, which does not require interim analysis.

Final analysis
The final analysis will be conducted when data from all randomized patients are available (n=112 per group). The conclusion will be based on the final posterior distributions (n=112 each). We will conclude noninferiority of NB compared to CT if the estimated probability of inferiority is less than 5%. We will conclude superiority of NB if the estimated probability that NB is better than CT is higher than 95%.

The median estimate and 95% credible interval will be given for the diagnostic accuracy for NB and for CT, as well as their difference. Additionally, we will estimate and report the probability that NB is non-inferior to CT and NB is superior to CT. These probabilities can be estimated using the posterior distributions of diagnostic accuracies.

Subgroup analysis:

Pre-hoc analyses of subgroups will include the groups defined by the two stratification factors, expertise of radiologist or pulmonologists, etc… The full list of subgroup pre-hoc analyses will be defined in the statistical analysis plan which will be completed and signed off by the trial steering committee prior to final patient entry and prior to any prior full analysis of the data. To allow for comparison of diagnostic accuracy and yield differences across subgroups (e.g., middle vs outer third), logistic regression models with interaction with treatment group will be fit.

Operating characteristics

With the Bayesian paradigm, there is no type I error rate. We conducted a simulation study to determine appropriate threshold for noninferiority conclusion and superiority conclusion at the final analysis. The operating characteristics of the proposed design under various scenarios for the true unknown parameter distributions were evaluated and shown in the below table. In this simulation study, we first postulated the true distribution of the diagnostic accuracy using a Beta distribution, which gives the specific mean and standard deviation. For example, Beta(141, 35) is used to represent a distribution with mean 0.80 and standard deviation (sd) 0.03. We used 0.60, 0.70, 0.80, and 0.90 as the mean and 0.01 and 0.03 as the sd. However, because different standard deviations yielded similar results, we only present the results for sd=0.03. The simulation size is 10,000 and the available decision in the simulation is: conclude non-inferiority at final analysis (> -10%). The following table shows its probability under various scenarios.

Design characteristics with final 10% (0.95)

						Final analysis	
True CT Mean	True NB Mean	True State	Difference			NB is non-inferior	NB is superior
0.7	0.6	Inferiority	-0.1			5.3	--
0.8	0.7	Inferiority	-0.1			4.7	--
0.9	0.8	Inferiority	-0.1			5.4	--
0.8	0.6	Inferiority	-0.2			--	--
0.9	0.7	Inferiority	-0.2			--	--
0.7	0.7	Non-inferiority	0.0			44.9	4.9
0.8	0.8	Non-inferiority	0.0			54.2	4.9
0.9	0.9	Non-inferiority	0.0			74.4	4.7
0.6	0.7	Superiority	0.1			47.0	46.5
0.7	0.8	Superiority	0.1			43.7	53.0
0.8	0.9	Superiority	0.1			31.7	67.8
0.6	0.8	Superiority	0.2			4.8	95.1
0.7	0.9	Superiority	0.2			1.3	98.7

Probabilities less than 1% are not shown.

6.3 Variables Recorded

- Past medical history
- Demographic data
- Smoking history
- Occupational history
- Current medications
- Laboratory data (complete blood count, electrolytes, creatinine, coagulation profile if available, results of fungal serologies if available)
- Chest CT characteristics:
    - Location of the nodule (lobe and segment)
    - Nodule size (longest axis)
    - Distance to the nearest visible bronchus on either CT plane (axial, coronal or sagittal)
    - Bronchus sign (airway aligned with nodule)
    - Distance to the nearest parietal pleura
- PET scan characteristics (FDG uptake (SUV))
- Procedural characteristics:
    - Duration of procedure
    - Number and type of biopsies
    - Use of FluoroNav, and divergence in mm if used
    - Radiation exposure
    - Complications (pneumothorax, bleeding, others)
- Time to procedure (delay between decision to biopsy and procedure)
- Time from identification of nodule to treatment for malignant nodules
- Need for another biopsy modality
- Need for an additional staging procedure
- Follow-up data.

7. Safety Reporting of Adverse Events

7.1 Grading

Adverse events will be graded according to the NCI's Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0, dated November 27, 2017, currently locatable via the following URL: <https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf >.

If events are not listed in the CTCAE, severity may be designated as mild, moderate, severe, life-threatening, or fatal which respectively correspond to Grades 1, 2, 3, 4, and 5 on the NCI CTCAE, with the following definitions:

- **Mild:** Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- **Moderate:** Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) such as preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc;
- **Severe:** Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL such as bathing, dressing and undressing, feeding self, using the toilet, taking medications;
- **Life-threatening:** Urgent intervention indicated to prevent risk of death present at the time of the event;
- **Fatal:** An event that results in the death of the patient.

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.

7.2 Reporting Period

The procedures being performed, bronchoscopy and CT-guided biopsy, are standard of care for management of indeterminate pulmonary nodules. Therefore, 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.
- After informed consent but prior to initiation of navigation bronchoscopy or CT-guided biopsy, serious and non-serious adverse events should be reported only if possibly, probably or definitely attributed by the patient's study physician to a protocol-mandated research procedure or intervention.
- The principal AE reporting period will be within 7 days of the study procedure, as it would be exceedingly uncommon for a new biopsy-related complication to occur more than 7 days after the biopsy procedure. Effort should be made on post-procedure day #7 to assess for any complications which have not already risen to investigator awareness.
- Any serious adverse event that occurs ≤ 7 days after initiation of navigation bronchoscopy or CT-guided biopsy, regardless of causality to participation in the study, must be reported to the Coordinating Center in an expedited fashion as directed below (Reporting Procedures).

During the 7-day reporting period, non-serious adverse events should only be recorded if, in the opinion of the investigator, there is a reasonable possibility the event is attributable to participation in the study. Non-serious adverse events related to navigation bronchoscopy or CT-guided biopsy or the next phase of the patient's treatment or management should NOT be recorded.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and the Coordinating Center of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

7.3 Procedure-related Risks

We do not expect additional safety concerns from this protocol over those incurred during navigation bronchoscopy and CT-guided biopsy, explained to all patients undergoing navigation bronchoscopy and CT-guided biopsy as part of clinical informed consent in the standard of care setting. These risks, inherent in the procedures themselves, include pneumothorax, bleeding, pain, or, rarely, infection. Risk of death is estimated around 1/10,000. We do not expect that enrollment in this study will result in an increased risk for the patient.

The greatest risks from bronchoscopy are related to sedation and maneuvering the bronchoscope into the patient's airway. Accordingly, a nurse and/or a respiratory therapist will monitor all patients during the procedure and full anesthesia support will be available. In addition, pulse oximetry, respiratory rate, blood pressure, ECG, and heart rate will be continuously monitored. Patients will not be released until they are fully awake and medically stable as per standard local standard of care operations.

Other risks include those associated with biopsy and are the same as for standard flexible bronchoscopy: pneumothorax, breathing difficulty, vocal cord spasm, vomiting, dizziness, bronchial spasm, infection, low blood oxygen, heart attack and bleeding from biopsied site. The occurrence of these risks is extremely low. The measures to mitigate the risks are the same as for all bronchoscopy. To minimize the chance of bleeding, all patients will be questioned about tendency to bleed prior to bronchoscopy as per standard care. Anticoagulation with antiplatelet agents will be held according to guideline recommendations for that drug. If bleeding occurs, patients will be treated with direct pressure, local instillation of iced saline or other bronchoscopic interventions as deemed necessary. Vocal cord spasm will be mitigated with the use of lidocaine on the vocal cords. Patients with lung disease may receive bronchodilators prior to bronchoscopy at the discretion of the performing bronchoscopist. Patients are given supplemental oxygen and their oxygen level is continuously monitored using pulse oximetry. If there is any sign of a worsening in status, such as elevated heart rate, low oxygen, or electrocardiogram (ECG) changes, the procedure will be aborted.

The risks associated with CT-guided biopsy include pneumothorax, breathing difficulty, infection, low blood oxygen, and bleeding from biopsied site. The predominant risk of this procedure is pneumothorax. The measures to mitigate the risks are the same for all biopsy procedures. To minimize the chance of bleeding, all patients will be questioned for their tendency to bleed prior to the procedure as per standard care. Anticoagulation with antiplatelet agents will be held according to guideline recommendations for that drug. If bleeding occurs, patients will be treated with direct pressure. Patients are given supplemental oxygen and their oxygen level is continuously monitored using pulse oximetry. A nurse, respiratory therapist and physician continuously monitor patients ECG, heart rate, blood pressure, and blood oxygen during the procedure. If there

is any sign of a worsening in status, such as a clinically significant elevated heart rate, low oxygen saturation, or ECG changes, the procedure will be aborted.

7.4 Research-only 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 applicable laws and regulations. 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.

7.5 Benefits

There is no guarantee that the subjects will receive any benefit from this study.

7.6 Definitions

7.6.1 Adverse Event (AE)

An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.
Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

7.6.2 Serious Adverse Event (SAE)

A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening;
- Requires or prolongs inpatient hospitalization;
- Results in persistent or significant disability/incapacity;
- Constitutes a congenital anomaly or birth defect; or
- Jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures.
- Elective or pre-planned treatment for a pre-existing condition that did not worsen.
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission.

- Respite care.

7.6.3 Expectedness

Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the study protocol or current adverse event list, in applicable information describing use of a marketed product in the standard of care setting (e.g. product manual, investigator's brochure, package insert) or is included in the informed consent document as a potential risk.

Unexpected: An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the study protocol or current adverse event list, in applicable information describing use of a marketed product in the standard of care setting (e.g. product manual, investigator's brochure, package insert) or when it is not included in the informed consent document as a potential risk.

7.6.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and participation in the study. Attribution will be assigned as follows:

- Definite – The AE is clearly related to study participation.
- Probable – The AE is likely related to study participation.
- Possible – The AE may be related to study participation.
- Unlikely – The AE is doubtfully related to study participation.
- Unrelated – The AE is clearly NOT related to study participation.

7.7 Reporting Procedures

7.7.1 General Considerations

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs, and avoid colloquialisms and abbreviations. If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g. record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death."

A pre-existing medical condition is one that is present prior to initiation of treatment or intervention specified by the protocol. Such conditions should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions; or
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study; or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

7.7.2 Serious Adverse Events

All serious adverse events, regardless of causality to study participation, will be reported to the Principal Investigator and/or the Study Coordinator at each institution, and also to the Coordinating Center.

All serious adverse events must be reported to the Coordinating Center within 24 hours of the investigator becoming aware of the event. Events should be reported using the Vanderbilt SAE form, located in the packet of supplemental forms. This form must be fully completed and emailed (preferred), faxed, or scanned to:

ATTN: VICC CTSR Personnel
EMAIL: Coordinating.Center@vumc.org
FAX: (615) 875-0040

If SAE documents are faxed, the Coordinating Center must be notified via email as well. Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

The Coordinating Center will disseminate information regarding serious adverse events to the participating sites as described in FDA guidance only in the case that the event(s) is/are unexpected, and is/are believed to be related (i.e., possibly, probably or definitely) to the study device/medication. The Coordinating Center will be responsible for reporting of events to supporters as appropriate (outlined below).

7.7.3 Institutional Review Board

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification of the study protocol, these modifications will be provided to the IRB as soon as is possible.

7.7.4 Reporting to Funder

Upon request from Medtronic, Vanderbilt University Medical Center acting as the Coordinating Center will notify Medtronic of any serious adverse event (SAE) that occurs during the reporting period as defined above in Section 7.2. Within 2 working days after the Coordinating Center initially receives the safety information from the site, the Coordinating Center will report the SAE (on the MedWatch, Medtronic, or Vanderbilt SAE form approved by the Coordinating Center and Medtronic) to a point of contact specified by Medtronic. Follow-up SAE reports received by the Coordinating Center should be sent within 2 working days to Medtronic using the same procedure used for transmitting the initial report.

8. Data Safety and Monitoring

8.1 Data Collection

The Vanderbilt University Office of Research will be used as a central location for data processing and management. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. 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. 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 940 other academic/non-profit consortium partners in 75 countries. Vanderbilt leads the REDCap Consortium, which currently supports more than 99,000 projects and 128,000 users.

8.2 Data and Safety Monitoring

The Vanderbilt-Ingram Cancer Center (VICC) oversees patient safety and data monitoring for its investigator-initiated and NIH-NCI funded clinical trials through its Data and Safety Monitoring Committee (DSMC). The purpose of the DSMC is to ensure the efficient implementation and management of the VICC Data and Safety Monitoring Plan (DSMP). The Committee maintains authority to intervene in the conduct of studies as necessary to ensure clinical research performed at VICC achieves the highest quality standards.

The VICC DSMC meets on a quarterly basis and ad hoc to discuss data and safety monitoring of clinical trials and to oversee the VICC DSMP. Internal audits for compliance with adverse event reporting, regulatory and study requirements, and data accuracy and completion are conducted according to the VICC DSMP according to study phase and risk. The committee reviews all serious adverse events (SAE) on Vanderbilt sponsored investigator-initiated studies on a quarterly basis and provides DSMC SAE review reports to the Vanderbilt IRB.

8.3 Data Handling and Record Keeping

An electronic case report form (eCRF) is required and must be completed for each included participant. The completed dataset should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from Vanderbilt.

To enable evaluations and/or audits from health authorities and Vanderbilt, the site investigator agrees to keep records including: The identity of all participants (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of any study drug or device disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

Queries resulting from review of the eCRFs will be generated for the site and corrections will be made by the study site personnel. This will be done on an ongoing basis.

9. Regulatory Considerations

9.1 Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per current institutional standards.

The trial will not be initiated until there is approval by the IRB of the protocol, informed consent document and any other material used to inform the patient about the nature of the trial. 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 sponsor-investigator and 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 any applicable local IRB and the sponsor-investigator (or designee).

The sponsor-investigator (or designee) is responsible for the coordination and development of all protocol amendments. Once approved by the sponsor-investigator, Vanderbilt will disseminate this information to the participating study sites.

9.2 Informed Consent

The investigator (or his/her designee) will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each participant will be informed that participation in the study is voluntary, that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect subsequent medical treatment or relationship with the treating physician(s) or institution.

The informed consent will be given by means of a standard written or in electronic format, written in non-technical language, which will be IRB approved. The participant should read and consider the statement before signing and dating it, and will be given a copy of the document. No patient will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

9.3 Ethics and 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.

9.4 Confidentiality

It is the responsibility of the investigator to ensure the confidentiality of patients participating in the trial and all of their medical information is maintained. 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.

9.5 Payment and Remuneration

Subjects will not be paid to participate in the study.

9.6 Costs

There will be no additional costs 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.

9.7 Study Termination

The sponsor-investigator reserves the right to terminate the study at any site and at any time. Reasons for study termination may include, but are not limited to, the following:

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

10. Study Coordination

10.1 Trial Compliance

This is an investigator-initiated study. The Principal Investigator, Fabien Maldonado, M.D. (who may also be referred to as the Sponsor-Investigator), is conducting the study and acting as the sponsor. Therefore, the legal and ethical obligations of the Principal Investigator include both those of a sponsor and those of a principal investigator.

Vanderbilt is the Coordinating Center for this study. All aspects of the study will be carefully monitored by the Coordinating Center for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

10.2 Changes to Protocol and Informed Consent Document

Any change to the protocol and informed consent document must be reviewed and approved by the Coordinating Center before being submitted to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) at participating institutions. Amendments should not be implemented until all necessary approvals have been obtained, except when necessary to eliminate an immediate hazard to study subjects.

10.3 Protocol Deviations

The Coordinating 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.

10.4 Monitoring and Quality Assurance

As the Coordinating Center, Vanderbilt has responsibilities to health authorities to take all reasonable steps to ensure the proper conduct of the study with regard to ethics, protocol adherence, integrity, validity of the data recorded on the CRFs, and adherence to regulations regarding Good Clinical Practice (GCP) and the protection of human subjects.

In accordance with applicable regulations, GCP, and Coordinating Center procedures, sites will be contacted prior to the start of the study to review with site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Coordinating Center requirements.
During the course of the study, the Coordinating Center will routinely monitor sites for protocol compliance, compare CRFs with original source documents from individual subjects, assess drug accountability, and ensure that the study is being conducted according to the pertinent regulatory requirements. The review of subject medical records will be performed in a manner to ensure that subject confidentiality is maintained. Monitoring visits will primarily be conducted remotely, and sites are required to provide the appropriate source documentation in order to allow for proper oversight per GCP. Investigators must agree to cooperate with the Coordinating Center to ensure that any problems detected are resolved.

10.5 Data Verification

Data will be collected via eCRFs and entered into the database per Coordinating Center guidelines. The Coordinating Center will check data accuracy by performing source data verification. Source data verification is a direct comparison of the entries made on the CRFs against the appropriate source documentation. This will be conducted remotely, with the possibility of on-site verification periodically. Discrepancies in the data will be

brought to the attention of the investigator and/or the investigator's staff. Any necessary corrections will be made directly to the eCRFs or via queries by the investigator and/or the investigator's staff.

10.6 Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The required documents include but are not limited to the following: IRB approvals (i.e., protocol, consent form, amendments, patient brochures, recruitment material, etc.), each participant's informed consent, enrollment form, eligibility checklist, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. Specified members at each participating site will submit all pertinent regulatory documents to the Coordinating Center, for storage in a secure location. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

10.7 Closure of the Study

The Coordinating Center reserves the right to discontinue a site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

10.8 Records Retention

FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study, including CRFs, consent forms, laboratory test results and physical exam, imaging and medical procedure records, must be retained by each site's Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the applicable national and local health authorities are notified.
Following closure of the study, each participating site will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

11. Publications

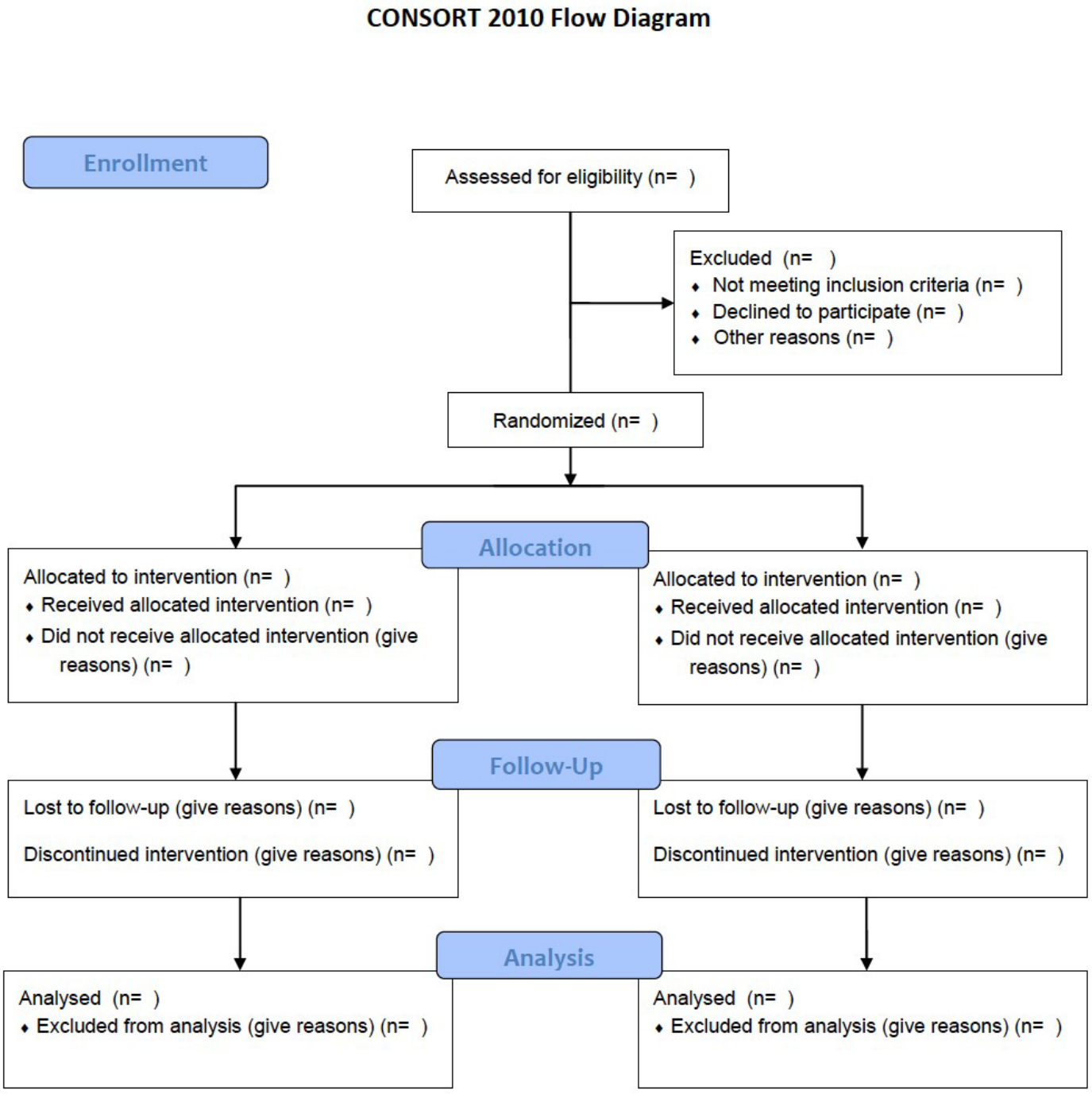
Any manuscript or releases resulting from the collaborative research must be approved by the sponsor-investigator and will be circulated to applicable participating sites/investigators prior to submission for publication or presentation. A publication plan consistent with the international Committee of Medical Journal Editors (ICMJE) will be created prior to analysis ad publication of any data. All data will be made available to

authors as required. The publication of sub-studies, post-hoc analyses, or single-center experiences will not precede the primary multicenter publication. Publication of results will be determined by the investigators, without limitations from the funder. Input (non-binding) will be obtained from the funder who will be given access to the data after closure of the study. All authors are expected to disclose financial or affiliations that could be considered conflicts of interest per journal or medical society requirements.

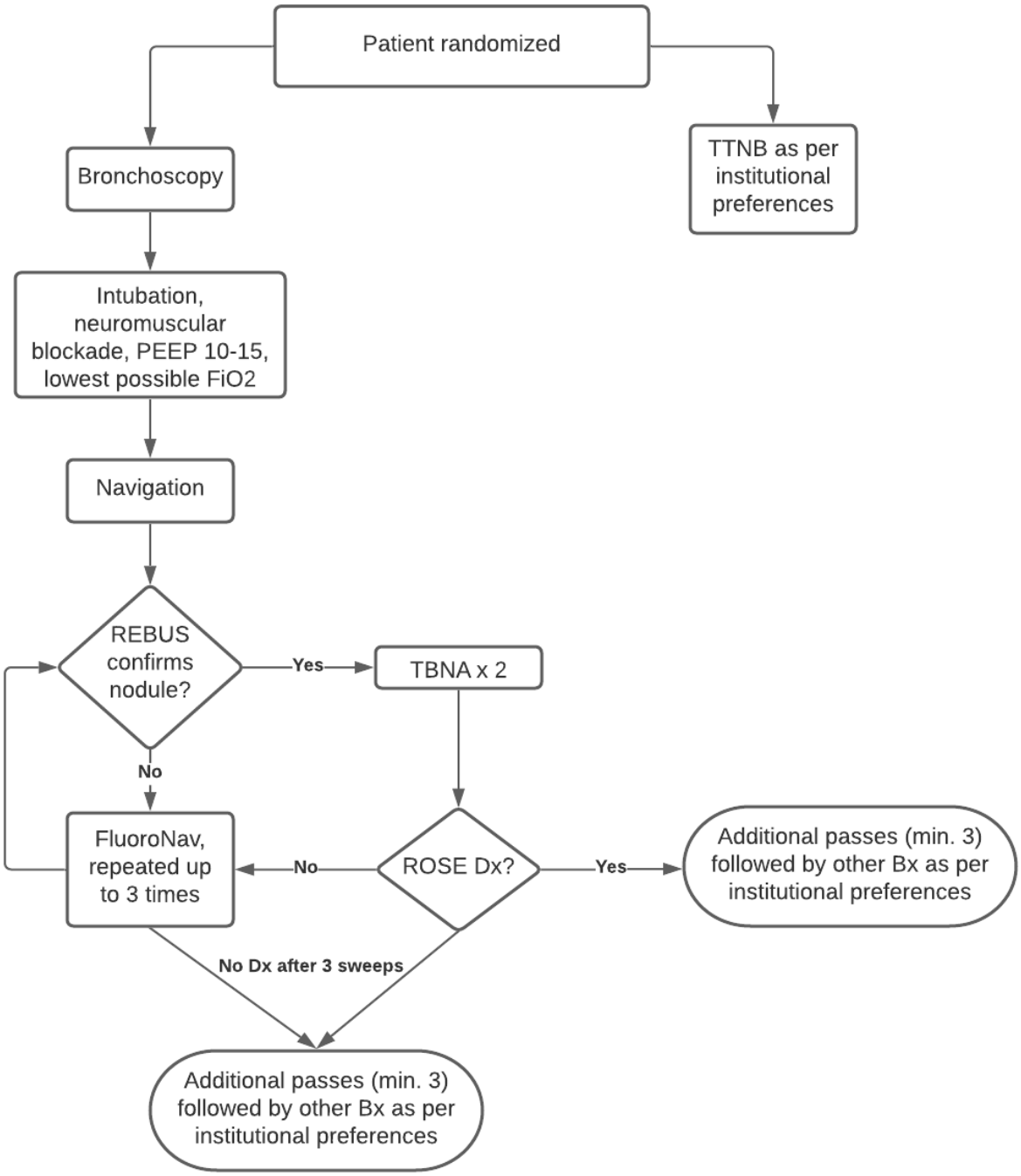
12. References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin.* 2017;67(1):7-30.
2. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med.* 2011;365(5):395-409.
3. Tanoue LT, Tanner NT, Gould MK, Silvestri GA. Lung cancer screening. *American journal of respiratory and critical care medicine.* 2015;191(1):19-33.
4. Gould MK, Tang T, Liu IL, et al. Recent Trends in the Identification of Incidental Pulmonary Nodules. *American journal of respiratory and critical care medicine.* 2015;192(10):1208-1214.
5. Gould MK, Fletcher J, Iannettoni MD, et al. Evaluation of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest.* 2007;132(3 Suppl):108S-130S.
6. Chang CY, Tzao C, Lee SC, et al. Incremental value of integrated FDG-PET/CT in evaluating indeterminate solitary pulmonary nodule for malignancy. *Mol Imaging Biol.* 2010;12(2):204-209.
7. Kothary N, Lock L, Sze DY, Hofmann LV. Computed tomography-guided percutaneous needle biopsy of pulmonary nodules: impact of nodule size on diagnostic accuracy. *Clin Lung Cancer.* 2009;10(5):360-363.
8. Ng YL, Patsios D, Roberts H, et al. CT-guided percutaneous fine-needle aspiration biopsy of pulmonary nodules measuring 10 mm or less. *Clin Radiol.* 2008;63(3):272-277.
9. Wiener RS, Schwartz LM, Woloshin S, Welch HG. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: an analysis of discharge records. *Annals of internal medicine.* 2011;155(3):137-144.
10. Ost DE, Ernst A, Lei X, et al. Diagnostic Yield and Complications of Bronchoscopy for Peripheral Lung Lesions. Results of the AQuIRE Registry. *Am J Respir Crit Care Med.* 2016;193(1):68-77.
11. Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. *Chest.* 2012;142(2):385-393.
12. Folch EE, Pritchett MA, Nead MA, et al. Electromagnetic Navigation Bronchoscopy for Peripheral Pulmonary Lesions: One-Year Results of the Prospective, Multicenter NAVIGATE Study. *J Thorac Oncol.* 2018.
13. El-Osta H, Jani P, Mansour A, Rascoe P, Jafri S. Endobronchial Ultrasound for Nodal Staging of Patients with Non-Small-Cell Lung Cancer with Radiologically Normal Mediastinum. A Meta-Analysis. *Ann Am Thorac Soc.* 2018;15(7):864-874.
14. McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules detected on first screening CT. *The New England journal of medicine.* 2013;369(10):910-919.
15. Herder GJ, van Tinteren H, Golding RP, et al. Clinical prediction model to characterize pulmonary nodules: validation and added value of 18F-fluorodeoxyglucose positron emission tomography. *Chest.* 2005;128(4):2490-2496.
16. Thiboutot J, Lee HJ, Silvestri GA, et al. Study Design and Rationale: A Multicenter, Prospective Trial of Electromagnetic Bronchoscopic and Electromagnetic Transthoracic Navigational Approaches for the Biopsy of Peripheral Pulmonary Nodules (ALL IN ONE Trial). *Contemporary clinical trials.* 2018;71:88-95.
17. Khandhar SJ, Bowling MR, Flandes J, et al. Electromagnetic navigation bronchoscopy to access lung lesions in 1,000 subjects: first results of the prospective, multicenter NAVIGATE study. *BMC Pulm Med.* 2017;17(1):59.

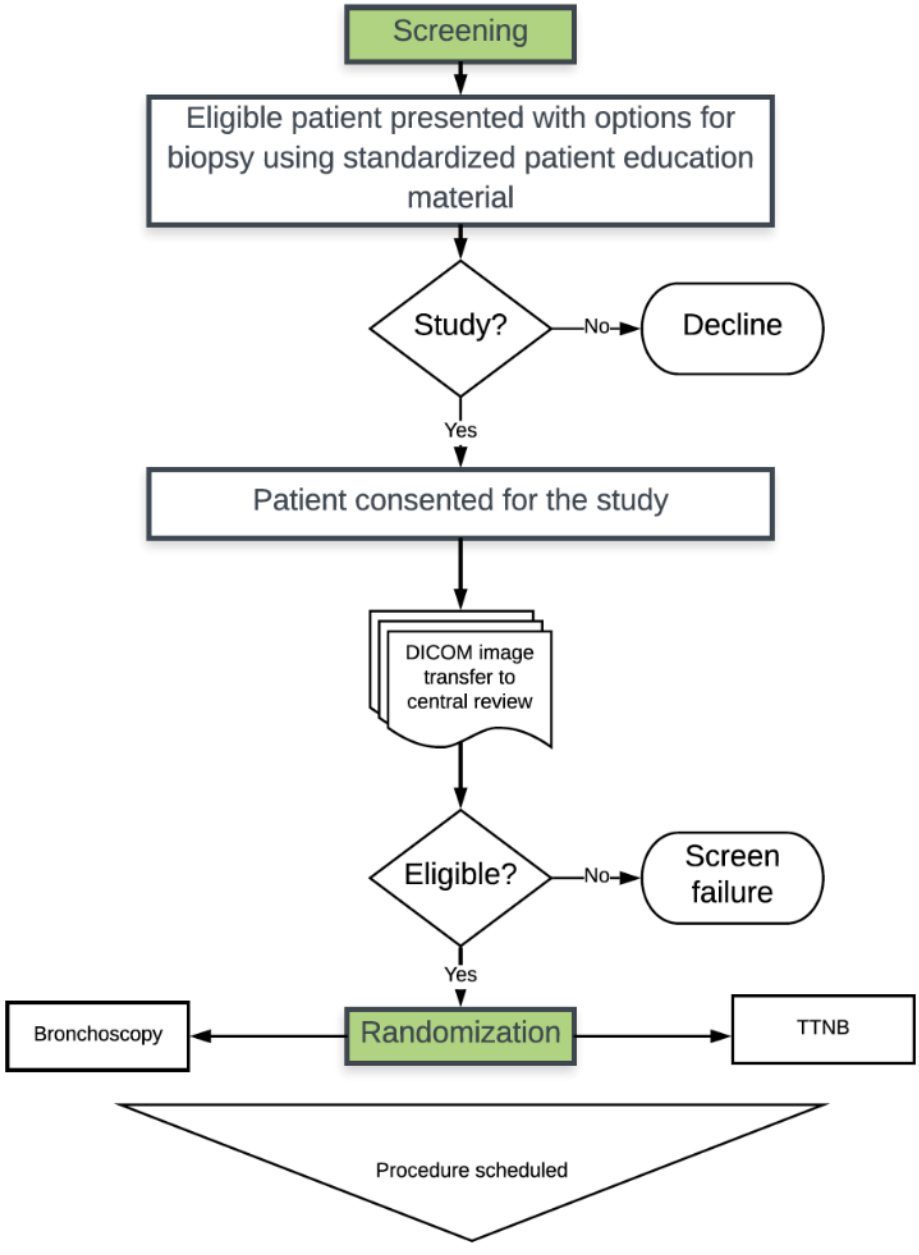
13. CONSORT Flow Diagram



14. Procedural Flow Chart



15. Screening Flow Chart



Patients who do not undergo the procedure because they decide not to will be considered screen failure

Patients who do not undergo the procedure because the operator decides not to proceed will be analyzed a intention to treat

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16. Study Assessment Table

Study procedures	Visit 1	Visit 2	Follow-Up (after Visit 2 bronchoscopy or CT-guided bx)			
			7 days* (+0-3d)	**3 months** (±14d)	**6 months** (±30d)	**12 months** (±30d)
Informed consent	1					
Inclusion/exclusion criteria	1					
Demographics	SOC					
Medical history	SOC					
Adverse events	1	1	1	1	1	1
Physical exam	SOC			SOC	SOC	SOC
Labs	SOC					
Pregnancy test (optional)	SOC					
Radiology review	1					
Pathology review			1 (review Visit 2 tissue)			
CT scan (chest)	SOC			SOC	SOC	SOC
Navigation bronchoscopy (randomized)		SOC				
CT-guided biopsy (randomized)		SOC				

* Between 7-10 days after initiation of navigation bronchoscopy or CT-guided biopsy (i.e. the standard of care procedure performed during Visit 2), each patient will subsequently receive at least one follow-up contact by telephone or clinic visit (or by chart review in the event of patient incapacitation).