Multicenter, prospective, randomized trial of bronchoscopy with ultrathin bronchoscope and radial endobronchial ultrasound (R-EBUS) with fluoroscopy versus standard fiberoptic bronchoscopy (FB) with fluoroscopy for biopsy of pulmonary lesions

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OBJECTIVES

The goal of this study is to evaluate radial endobronchial ultrasound (R-EBUS) for the diagnosis of pulmonary lesions (≥1.5cm). Accessing pulmonary lesions is problematic because they are often not visible endobronchially, may not be large enough to be easily visualized by fluoroscopy for transbronchial biopsy (TBBx), and/or are surrounded by damaged lung making the transthoracic approach difficult. In this study, we hope to evaluate new technologies to aid in transbronchial biopsy using R-EBUS to facilitate location and sampling of tissue.

SPECIFIC AIMS:

1. To compare the diagnostic yield of R-EBUS with the BFP190 ultrathin bronchoscope and fluoroscopy versus standard fiberoptic bronchoscopy (FB) with fluoroscopy in the evaluation of lung lesions 1.5-5cm.
2. To assess factors that may influence yield:
    a. radiographic characteristics – size, location, distance from visible bronchus, PET characteristics
    b. procedural characteristics – number of passes, type of specimen obtained [brush, forceps biopsy, site of biopsy (within vs. adjacent to lesion), rapid on-site evaluation (ROSE) diagnosis

I. BACKGROUND

Pulmonary lesions are a common but difficult issue for primary care and specialty physicians and are often found incidentally on Chest X-Ray (CXR) or Computed Tomography (CT) scan.[1] With the results of the National Lung Cancer Screening Trial demonstrating a reduction in lung cancer mortality with screening of high risk patients with low dose CT scan, the number of nodules detected requiring follow up is likely to increase exponentially as 25% of those screened had a detected lung abnormality. [2] In studies of incidentally detected nodules, the prevalence of malignancy ranges from 2-82% [3], the problem for clinicians is deciding on the management and further diagnostic modalities to pursue.

Current recommendations from the American College of Chest Physicians (ACCP) evidence-based guidelines for the management of pulmonary lesions begin with the determination of whether the lesion is stable or has benign calcification. [1,4] If the lesion is stable or benign, no further evaluation is warranted; otherwise, management decisions are based on surgical risk and on the clinical probability that the lesion is malignant. For patients with <5% probability, repeat imaging is recommended at variable time intervals up to 2 years, and for patients with high probability of cancer (>65%), tissue diagnosis with VATS followed by resection is recommended. Those patients with lesions of intermediate probability for malignancy require more complicated evaluation.

The various recommended procedures for obtaining tissue diagnosis in these intermediate cases include transthoracic needle aspiration (TTNA), surgery, and flexible bronchoscopy (FB). The diagnostic yield with FB varies with lesion size and location. Based on review of 10 studies using FB for diagnosing peripheral pulmonary nodules (PPN), the sensitivity is only 34% for lesions <2cm and has been found to be as low as 14%. [5,6] The sensitivity increases to 63% when lesions are >2cm in size, but decreases as the distance from the hilum increases. A lesion having a bronchus sign (the finding of a CT-visible bronchus leading to the lesion) increases the success of transbronchial biopsy and brushing. [7] The ACCP recommends that nodules without a CT-bronchus sign should be pursued with TTNA unless radial endobronchial ultrasound (R-EBUS) is available.[6] Bronchoscopy is commonly used for pulmonary masses, but the yield, while high, does not approach 100%.

Several new technologies have evolved which allow clinicians to reach pulmonary lesions with bronchoscopy: electromagnetic navigation (ENB), ultrathin bronchoscope, R-EBUS, virtual bronchoscopy (VB), endobronchial ultrasound (EBUS), and guide sheath.

ENB was designed to guide the bronchoscope and the physician to peripheral lesions, and has been likened to a global positioning system (GPS) for bronchoscopy. The four components necessary for ENB are an electromagnetic location board, a locatable sensor probe with steering that allows navigation through the bronchi, an extended working channel, and computer software that creates the VB images.[8] This is a real-time navigation system which has been found to have a diagnostic yield of 69-74% for PPN of any size and a pneumothorax rate of 0-7.5%. [8-12] Drawbacks of ENB include the high cost to purchase all the components, the need for extensive training and the complexity of the system for the general pulmonologist.

EBUS has been evaluated for diagnosing and staging lesions, as a tool to assess both central and peripheral lesions, and to evaluate various layers of bronchi. [13-15] Linear EBUS has been shown to be effective for biopsy of mediastinal and hilar adenopathy for diagnosis and staging of potentially metastatic lung cancer, [16] but radial EBUS can be used to locate more peripheral pulmonary lesions for transbronchial biopsy. [17-22] With the addition of a guide sheath (Olympus Inc.) to maintain the position of the bronchoscope within/near the target lesion, the diagnostic yields range from 58% to as high as 86%, which is comparable to CT-guided TTNA. [17-19,22,23] The use of ultrasound allows real-time visualization outside the tracheobronchial tree and eliminates the risk of radiation exposure.

A recent meta-analysis that included 39 studies of guided-bronchoscopy technologies for the diagnosis of pulmonary nodules demonstrated a pooled diagnostic yield of 70%, which is higher than the yield for traditional transbronchial biopsy. [24] The yield increased as the lesion size increased. The pneumothorax rate was 1.5%, which is significantly smaller than that reported for TTNA. This study demonstrated that the diagnostic yield

of guided bronchoscopic techniques is better than that of traditional transbronchial biopsy for tissue sampling of pulmonary nodules; however, it concluded that further study is needed to determine its role in the evaluation of peripheral pulmonary lesions. The yield for bronchoscopy using R-EBUS with or without guide sheath is 73.4% and 71.6%, respectively.

RATIONALE
Despite new technologies that have arisen in the last decade for bronchoscopic biopsy of peripheral pulmonary lesions, the sensitivity for FOB remains as low as 34% for lesions < 2cm and increases to around 63% for lesions >2cm in size, but decreases again as the distance from the hilum increases. The use of R-EBUS as an adjunct is recommended as it increases diagnostic yield. A biopsy approach using R-EBUS through an ultrathin scope, guide sheath and fluoroscopy may increase the diagnostic yield of pulmonary lesions even further when compared to standard FB with fluoroscopy; it may also improve the utility of bronchoscopy for the diagnosis of peripheral pulmonary lesions thereby decreasing the need and risk associated with TTNA. This study will also evaluate the radiographic and procedural factors that have been described to influence that diagnostic yield.

II. RESEARCH DESIGN AND METHODS

This is a multi-center, prospective, randomized controlled trial to evaluate the diagnostic yield of two standard of care bronchoscopy procedures used to biopsy peripheral pulmonary lesions identified on chest CT: (1) standard FB using an adult standard bronchoscope (Olympus BF-180) with fluoroscopy, and (2) bronchoscopy using the BFP-190 ultrathin bronchoscope in combination with R-EBUS and guide sheath.

Primary outcomes: Diagnostic yield of standard FB with fluoroscopy using standard adult bronchoscope versus bronchoscopy using ultrathin bronchoscope in combination with R-EBUS with or without guide sheath for lung lesions 1.5-5 cm.

Secondary Outcomes:

1) The radiographic and procedural factors that influence the diagnostic yield including the size and location of the lesion, the distance from the main carina, the number and type of specimens obtained, and the location of sampling within the lesion.
2) Adverse event rates of hemoptysis and pneumothorax.

DEFINITIONS:
Lung lesions: solid nodules or masses 1.5-5 cm in diameter

SUBJECT ENROLLMENT (See Figure 1):
Subjects presenting to their standard of care pulmonologist in need of a bronchoscopic biopsy of their peripheral pulmonary lesion as part of their standard medical care, and who meet study inclusion/exclusion criteria, will be invited to participate. A total of 214

patients will be enrolled. As this is a competitive enrollment study, MUSC will enroll up to 75 volunteers. Eligibility will be determined by each site PI. The PI or Co-I will explain the study to qualified subjects prior to obtaining consent. The subject will also be given an opportunity to review and sign documentation of HIPAA compliance and authorization.

Inclusion criteria:

Patients to be included for participation in this study are:

1) Patients with a solid lung lesion 1.5-5cm identified on chest CT (obtained within previous 3 months) with the intention to undergo bronchoscopic evaluation. If the lesion is partially solid (i.e. there is a ground glass component) then the solid portion must make up >75% of the lesion and measure at 1.5-5cm.The decision to pursue biopsy will be made by the treating physician and agreed upon by the patient. This will include patients determined to have an intermediate risk of malignancy (5-65%) and those non-surgical candidate with higher risk lesions in need of diagnosis for alternative treatment. OR
2) Patients with a solid lung lesion 1.5-5cm identified on chest CT (obtained within previous 3 months) that are surgical candidates with a high probability of cancer (>65%) will be referred for surgical evaluation. If the lesion is partially solid (i.e. there is a ground glass component) then the solid portion must make up >75% of the lesion and measure at 1.5-5cm. If the patient refuses surgery or if the surgeon requests a definitive diagnosis prior to surgery the patient will have the option to be included in this study. All sites will use the same online calculator to document probability of malignancy.
3) Patients whose targeted lung lesion is visualized with fluoroscopy
4) Are at least 22 years old,
5) Lack Bleeding disorders, and
6) Are able to provide informed consent.

Race and gender inclusion will reflect the population characteristics found in the respective regions.

Exclusion criteria:

Patients to be excluded from participation in this study are:

1) Patients with a pure ground-glass opacity identified on chest CT
2) Patients with endobronchial involvement seen on chest CT.
3) Patients who refuse to participate,
4) Are less than 22 years of age,
5) Lack fitness to undergo flexible bronchoscopy as determined by the bronchoscopist prior to procedure, and
6) Are unable to provide informed consent
7) Pregnant

INFORMED CONSENT:
Informed consent will take place in a private environment (e.g. patient exam room), free from distractions. The PI or sub-PI will approach the subject at their standard of care clinic appointment or prior to their scheduled bronchoscopy and will explain the study to qualified subjects prior to obtaining consent. All individuals who obtain consent (PI, Co-I, and study coordinators) have completion certificates for the CITI Human Subjects Research Education Course. Interviews to obtain consent will not follow any stressful situation (e.g. patient being informed he/she may have cancer) and will not be conducted if patient has received any mind-altering medications or anesthesia. Patients will be assessed for their capacity to consent by the ability to show comprehension of the procedure, ask appropriate questions, and appear properly oriented. A signed copy of all consents and the HIPAA authorization document will also be given to consenting subjects.

SUBJECT RANDOMIZATION
Once informed consent is obtained, the site PI will open the next randomization envelope to reveal the assigned procedure. Randomization envelopes are provided by MUSC and are to be opened in order, as indicated by the numbering on the exterior of the envelope. Inside each envelope is the randomization assignment for that subject. The randomization schedule is determined in advance by a computer with the plan for 1:1 randomization overall.

BRONCHOSCOPY PROCEDURES:
Patients will be randomized in a 1:1 fashion (107 in each arm) to undergo (1) standard FOB with fluoroscopy, or (2) R-EBUS with ultrathin bronchoscope (4.2 mm outer diameter with a 2 mm working channel) and guide sheath. This sample size will provide 85% power to detect a 20% improvement in yield using R-EBUS with fluoroscopy. This assumes a diagnostic yield for standard FB with fluoroscopy of 50% and R-EBUS with fluoroscopy is 70%. This also assumes 2-sided hypothesis testing and an alpha level (i.e. significance level) of 0.05.If subjects have multiple pulmonary lesions, it will be predetermined which lesion will be targeted. After informed consent and randomization have been performed, the following will occur:

(1) *Prior to bronchoscopy*: CT images will be obtained within 3 months of bronchoscopy and readily available for viewing during the bronchoscopic procedure. A de-identified copy of the CT and/or PET/CT report will be sent to the coordinating site (MUSC).

- *(2) At bronchoscopy*: Moderate or deep sedation will be administered as deemed clinically appropriate by the procedure team. The time the bronchoscope is inserted and removed will be recorded. When sufficient sedation has been given, the bronchoscope (standard adult FB (Olympus BF-180 or 190) or ultrathin depending on randomization) will be introduced into the airway. Topical anesthesia with 1%- 2% lidocaine will be administered to the vocal cords,

trachea, and right and left mainstem bronchi through the bronchoscope. The bronchoscope will be advanced as distally as possible under direct visualization. In cases in which the lesion cannot be located, the clinical judgment of the site PI will direct one or more of the following choices:

- abort the procedure
- crossover to standard bronchoscopy and brushing
- BAL under fluoroscopy (even when lesion is not visualized under ultrasound)
- another standard of care procedure

(3*) For Bronchoscopy plus R-EBUS:*
Once the ultrathin bronchoscope has been passed as distally as possible, the R-EBUS will be utilized. Depending on the number of generations of bronchi that are passed, a guide sheath (Olympus; external diameter 2mm [K201]) may be inserted into the ultrathin scope. The 20MHz mechanical R-EBUS probe (Olympus, UM-S20-17S) +/- the guide sheath covering will be introduced into the working channel of the bronchoscope and advanced to the lesion. An attempt to definitively locate the lesion with R-EBUS will be made. Fluoroscopy will be used to aide in locating the lesion, which will then be verified by R-EBUS. A de-identified jpeg image of the ultrasound image will be recorded and subsequently uploaded to the REDCap study data collection instrument. Once the lesion is located, the R-EBUS probe will be removed. The guide sheath will remain in place. Bronchial brush (Olympus BC-204D-2010 followed by a smooth transbronchial biopsy forceps (Olympus FB-233D) will be introduced through the working channel with guide sheath to obtain pathologic and cytologic specimens. 1 brushing (standardized to 10 strokes per brushing)will be performed followed by 5 transbronchial forceps biopsies. (Brush preparation: smear brushing sample, then cut brush and drop into cytolyte; fix slide with alcohol.) The R-EBUS probe will be reinserted after obtaining specimens to again verify the location of the lesion.

If the ultrasound image seen following R-EBUS probe insertion is eccentric, a double hinged curette will be inserted into the working channel in an attempt to manipulate the position such that the ultrasound image of the lesion becomes concentric.

If the bronchus identified on imaging cannot be reached by bronchoscopy, a double-hinged curette will be inserted into the working channel with the guide sheath, manipulated and directed to the bronchus and advanced with fluoroscopic guidance. The curette will be removed and the R-EBUS probe will be reinserted through the working channel with the guide sheath to confirm the location within the lesion. Once the targeted airway/lesion has been reached, biopsy specimens will be obtained with fluoroscopic imaging to verify positioning at the lesion. TBBx and brushing will be performed.

(4) *For Standard Bronchoscopy with Fluoroscopy:*
Once the standard FB (Olympus BF-180 or 190) is extended out into the airway as distally as possible, fluoroscopy will be used to aide in locating the lesion. Standard bronchial brush and standard smooth transbronchial biopsy forceps will be introduced to

obtain pathologic and cytologic specimens. One brushing (standardized to 10 strokes per brushing) will be performed and placed on a slide for Rapid On-site evaluation by pathology. Five transbronchial biopsies will then be performed under fluoroscopy. Rapid On-Site Evaluation (ROSE) is performed for all subjects randomized to standard bronchoscopy.

(5) Following both bronchoscopy procedures:
A portable chest X-ray will be performed to look for pneumothorax.

(6) *For Non-diagnostic (including chronic inflammation) Procedures (either arm):*
If a diagnosis is not obtained after the procedure, further recommendations regarding treatment will be made by the treating physician. (i.e. follow-up CT chest, CT guided transthoracic needle aspiration, or surgery). In the standard FB arm, the bronchoscopist will have the option of using peripheral ultrasound with or without the ultrathin scope to attempt to identify the lesion. Specimens obtained must be kept separate and identified as having performed using R-EBUS (e.g. labelled “radial brush”, “radial biopsy”) and reflected in the case report form. If ROSE is non-diagnostic and/or indicates chronic inflammation, crossover to the Ultrathin bronchoscope with R-EBUS will take place. In those patients that cross over to the Ultrathin bronchoscope with R-EBUS the same protocol for those randomized to the ultrathin/R-EBUS arm will be followed (see #3).

RISKS OF PROCEDURES:
The greatest risks from bronchoscopy are related to moderate or deep sedation and the very act of passing a bronchoscope into the airway. To mitigate risks of bronchoscopy all patients will be monitored by a nurse and a respiratory therapist during the procedure. In addition, oxygen saturation (using 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.

The risks associated with bronchoscopy are collapsed lung, 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. [25]If bleeding occurs, patients will be treated with direct pressure, local instillation of epinephrine or electrocautery. Vocal cord spasm will be prevented through 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. There is no way to reduce the minimal risk of infection due to bronchoscopy since the scope must go through the naso or oropharynx. Patients are given supplemental oxygen and their oxygen level is continuously monitored using pulse oximetry. Patients ECG, heart rate, blood pressure, and blood oxygen are continuously monitored by a nurse, respiratory therapist and physician during the

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

RESEARCH ONLY RISKS

Risk of breach in confidentiality

Every effort will be made to protect the privacy of the research subjects. All information and data related to this study will be maintained in secured, protected space, and access will be restricted to study personnel only.

DATA COLLECTION:

Prior to each site initiation, the site PI and staff will participate in an educational teleconference with the Coordinating Site PI to ensure that all personnel fully understand the protocol, data collection instrument, and any other study related issues or documents. Contact information, including the phone and pager numbers for the principal investigators and study staff will be provided to all sites

Data on the following will be collected at all sites: radiographic characteristics, procedural characteristics, diagnostic yield, crossover to other procedures, confirmation of diagnosis, and complications:

(1) *Radiographic Information*:

The radiographic information collected will include location of the lesion, size of the lesion, distance from a visible bronchus, and PET characteristics. For R-EBUS procedures, a jpeg ultrasound image of the lesion will be recorded, anonymized, and uploaded to the REDCap study data collection instrument. The location of the lesion (side, lobe and segment, i.e. right upper lobe anterior segment, etc.) will be determined and recorded. The size of the lesion in longest axis diameter will be measured and recorded. The distance from the trachea as calculated as the number of generations from the main carina (first generation) to the lesion will be recorded. All central and peripheral lesions considered intermediate risk will be included. If the patient has undergone a PET, the metabolic activity (measured SUV) will be recorded.

(2) *Procedural Characteristics*:

The procedural information will include the number of biopsy passes, types of biopsy performed (TBBx, , brush, BAL), and R-EBUS description of site of biopsy of the lesion (within vs. adjacent to) will be recorded. The time length of procedure, type and amount of sedation administered will also be recorded.

(3*) Diagnostic Yield and Crossover Procedures:*

Primary outcome of diagnostic yield will be determined from the results of the bronchoscopy. A biopsy that results in a specific diagnosis, either malignant or benign, will be assumed to be a true positive. Plan for further diagnostic management for patients who have a non-diagnostic biopsy (and/or biopsy indicating chronic inflammation) will be determined by the attending physician. Those patients will be followed for up to one year until a definitive diagnosis has been made (such as from

surgical pathology), or the lesion has decreased on repeat CT imaging. Under standard procedure randomization, if ROSE indicates chronic inflammation, crossover to R-EBUS will take place.

(4) *Confirmation of Diagnosis*:
Confirmation of the diagnosis by surgery or repeat imaging will be recorded for those patients who have non-diagnostic results (including chronic inflammation) from the study procedures. If the patient is referred for surgery, the surgical pathology will be considered the final diagnosis. If the patient has follow-up imaging that shows resolution of the lesion, the lesion will be determined to be of benign etiology. To verify final diagnosis, a copy of the final pathology report from bronchoscopy and any pathology reports from subsequent surgical resection, will be de-identified and provided by the site to the coordinating center.

(5) *Complications:*
Adverse event rates will be documented. Pneumothorax will be documented by post-biopsy CXR or chest ultrasonography, and the number requiring intervention, such as chest tube placement, will be recorded. Significant hemoptysis will be defined as bleeding noted at the time of procedure that requires a change in the level of care (e.g. outpatient to inpatient or inpatient to ICU) or a blood transfusion. Other adverse events that are common to bronchoscopy described above in “Risks” section will be monitored and reported by the patient or nursing staff.

DATA SAFETY MONITORING PLAN
All subjects enrolled in the trial will undergo routine standard of care bronchoscopy that is indicated a medically necessary by their physicians. Prior to the bronchoscopic procedure, PIs will explain the risks associated with bronchoscopy, and verify that the research only risks have been explained, and that the subject has signed an informed consent form. There are no anticipated risks, outside of the risk for the standard of care procedures for this clinical trial. All subjects are required to read, understand, and sign the informed consent form associated with the research study. Each subject will be informed of post procedure symptoms of which to be aware that may represent adverse reactions to the bronchoscopy. Symptoms that the patient will be informed to look out for include:

- Pain or difficulty with swallowing
- Difficulty breathing
- Vomiting
- Dizziness
- Abdominal or chest pain
- Continuous bright red blood in your sputum
- Fever above 100.0 degrees Fahrenheit

If the subject notes any of these symptoms, he/she is instructed to contact his/her physician, who will determine the course of action. All events are to be reported within 48 hours of occurrence to the coordinating site (MUSC). All adverse events (AEs) will

be reviewed by the medical monitor within one month of their occurrence and summarized for review. The PI at each site will be responsible for submitting this report to the IRB at his/her institution as required. AEs and other reportable events are defined below.

Reportable Events

(1) AEs

AEs will be defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Serious Adverse Events (SAEs) will be defined as any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

* results in death;
* is life-threatening;
* requires inpatient hospitalization or prolongation of existing hospitalization;
* results in a persistent or significant disability/incapacity;
* results in a congenital anomaly/birth defect; or
* any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Site PIs will be responsible for identifying adverse events during the procedure and during the standard of care follow-up period. Site PIs will review adverse events experienced by subjects treated at their site during the procedure standard of care follow-up period and will record them in the medical record. Site PIs will review all adverse events, expected or unexpected, per standard medical care.
Site PIs will classify AEs as expected or unexpected, and report AEs directly to the IRB per local IRB reporting policy. The lead investigator will capture all AEs occurring at all sites, including unanticipated AEs, in the REDCap data collection instrument.

(2) Protocol Deviations

Site PIs will be responsible for identifying and reporting all protocol deviations to the local IRB per local IRB reporting policy. The lead investigator will capture protocol *deviations occurring at all sites in the REDCap data collection instrument.*

(3) Protocol Amendments or Revisions

Amendments or revisions to the protocol proposed at all sites will first be approved by the lead investigator.

DATA STORAGE AND MAINTENANCE:

Each site investigator will review the results, and the results will become part of the subject’s medical record and research record. Any clinical follow-up or repeat procedures will be dictated by the patient’s physician based on clinically relevant data and will not be influenced by enrollment into this study. To protect subject

confidentiality, MUSC will receive all sites' data as de-identified through use of the 6 digit patient codes. All information and data related to this study will be stored in a secured, locked cabinet in MUSC Clinical Sciences Building Room 809. The privacy of subjects will be protected using a 6 digit computer generated random code. The key to the code will be kept in a password protected folder on the MUSC DB2 (\\DA) server; access to this folder is restricted to study personnel alone.

Electronic Data will be entered and stored in the secure REDCap database created for this study. REDCap is a web-based application designed exclusively to support data capture for research studies. It provides an intuitive interface for data entry, audit trails for tracking data manipulation and export procedures, procedures for importing data from external sources, advanced features such as branching logic and calculated fields, and automated export procedures for seamless data downloads to common statistical packages such as SPSS, SAS, Stata, and R. It was developed at Vanderbilt University (see http://redcap.vanderbilt.edu/consortium/index.php) and is ideal for remote data entry, as will be the case for this multi-center trial.

III. STATISTICAL ANALYSIS:
Statistical comparisons will be made using chi-square analysis where applicable. Sensitivity, specificity, positive and negative predictive value and accuracy of all procedures will be calculated. A logistic regression analysis of factors influencing tissue quantity will be undertaken.

Coordinating Center: MUSC will be the designated coordinating center for this trial. MUSC will be responsible for development of the database, housing the data, working with the sites on IRB issues, patient enrollment, completion of on-line data collection instrument and validation of the data. MUSC will also be responsible for payment to the sites when a patient's case report form is complete and query-free. Statistical support and interim analysis will be performed at MUSC by an in house statistician (Paul Nietert, PhD). Interim results will be shared with all participating sites during teleconference meetings.

Note: **The Medical University of South Carolina is the coordinating center for the study and there will be up to 8 collaborating centers participating in the study.** This study will be completed using a competitive enrollment strategy. That is sites will be paid on a per patient enrollment basis after completion of the procedure and case report form. The coordinating center has budgeted the time and resources necessary to manage this number of sites. Further, author placement on manuscripts (after first and senior authorship) will be dependent on enrollment such that the more patients a site enrolls, the earlier their PI's name will appear on the author list.

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Figure 1: Study Design