Study Title: Evaluation of 19-gauge vs 21-gauge EBUS TBNA in assessing thoracic lymphadenopathy

NCT # NCT03657849

Participant Contact Narrative: Evaluation of 19-gauge vs 21-gauge EBUS TBNA in assessing thoracic lymphadenopathy

1. Summary:

Endobronchial ultrasound-guided transbronchial needle aspirate (EBUS-TBNA) is a technique used to take samples of body tissue inside the chest without having to undergo an operation.
During this procedure, a special telescope (called a bronchoscope) is inserted through the mouth into the airways. Ultrasound technology allows the doctor to see the structures just outside the airway. By being able to see the structures outside the airway, the doctor is able to safely pass a fine needle through the airway to take samples of abnormal tissue.

EBUS-TBNA is used to take samples of tissue from the mediastinum. The mediastinum is the part of the chest between the lungs, and contains the heart, gullet, windpipe and lymph nodes. This area of the body is usually difficult to access without open surgery, hence the use of EBUS-TBNA. EBUS-TBNA may be used to investigate enlarged lymph nodes. This may be due to tuberculosis, sarcoidosis or cancer.

Currently, smaller 21-gauge and larger 19-gauge needles are used during the EBUS-TBNA procedure at Regions Hospital. The purpose of this study is to find out which needle is better in finding the explanation for the enlarged lymph nodes, minimizing complications and any follow up procedures that may be necessary if we are unable to get enough tissue during the EBUS-TBNA procedure (surgical sampling, radiological sampling, and/or follow-up imaging).

2. Study Aims:

Using the larger 19-gauge needle instead of 21-gauge needle during EBUS TBNA will have higher yield without increasing complications

Primary outcome:

- 19-gauge needle yield vs 21-gauge needle yield (true positive + true negative)/total)

Secondary outcome:

- Number of adequate samples by rapid onsite evaluation (ROSE)
- cytology assessment of sample size
- adequacy for molecular testing for lung cancer

H1: 19-gauge needle will have at least 7% higher absolute yield than 21-gauge needle (current yield for 21-g needle is 83%)

3. Background, Rationale, Significance:

Endobronchial ultrasound (EBUS) transbronchial needle aspiration (TBNA) is regarded as the preferred initial sampling method in assessment of mediastinal and hilar lymph adenopathy [1]. There are several needle sizes available commercially (25-, 22-, 21-, or 19-gauge). The size of the needle may affect the

quantity of tissue obtained, degree of tissue trauma, and amount of aspirated blood; each of which can affect the diagnostic yield.

The 2016 CHEST guidelines [2], recommended the use of either 21- or 22-gauge needle during EBUS TBNA due to similar performance in the published literature but were unable to comment on other needle sizes due to lack of data. Since then few retrospective publications evaluated the recently available 19-gauge needle [3-8]. Biswas et al. repeated EBUS TBNA using 19-G needle in addition to 21-G needle for those patients with an initial negative 21-G EBUS TBNA but have high suspicion for sarcoidosis. The 19-G needle identified granulomas in all 11 patients compared to only 2 in the 21-G needle [4]. All these publications showed similar safety to smaller needles without increased bleeding risk.

One of the drawbacks of EBUS TBNA is the loss of the histological structure due to smaller needle size, leading to lower yield in diagnoses that require preserving the cell structure to make the diagnosis, such as lymphomas (yield 68%) and sarcoidosis (yield 78%) compared to malignancy (yield 90%) [2, 9].

When EBUS does not yield diagnosis, or doesn't provide adequate tissue for molecular testing, patients are usually subjected to further diagnostic testing including repeat imaging studies, and commonly proceeding with more invasive procedures or surgical operations to obtain tissue, which in addition to delaying the diagnosis, causes significant distress for the patients and increase the cost.

We believe that using 19-G needle during EBUS TBNA will improve the diagnostic yield overall and lead to more rapid diagnosis with fewer procedures for the patients which would improve patient's satisfaction and decrease overall cost. The use of a 19-G needle could also result ultimately in fewer total passes which would typically result in less time under sedation for the patient.

4. Approach:

a. Study design:

This is a prospective, diagnostic accuracy study. For each lymph node sampled, we will alternate between the 19-g and the 21-g with each pass. Typically, an average of 5 passes is done in each lymph node (though number ranges from 3-12 based on physician judgment), for the study a minimum of 3 passes with each needle will be requested to provide adequate tissue for comparison. The choice of needle for the first pass will be randomized. More passes will be allowed with alternating needles based clinicians' judgment. Tissue obtained with the 19-g needles will be compared to tissue obtained with the 21-g needles with regards to diagnosis yield and adequacy for molecular testing.

b. Population:

i. Inclusion/Exclusion criteria

Inclusion:

- Age 18 years or older
- Able to provide informed consent
- Referred for EBUS TBNA sampling at Regions Hospital

Exclusion:

- On therapeutic warfarin, plavix or ticagrelor in the last 5 days

- INR >1.8, platelets <50K (evaluated at enrollment if patient has had them drawn as part of standard of care)

ii. Sample size:

A total of 50 patients will be enrolled, with an average of 1.7 lymphnodes sampled in each patient. Patients will be a convenience sample of patients referred to have the EBUS-TBNA procedure at Regions Hospital during the study period.

c. Data collection process

i. Process steps for identification of patients or records

All patients referred for EBUS TBNA sampling at Regions Hospital who meet the inclusion/exclusion criteria will be approached to be enrolled. These patients will be identified by one of the study investigators. Of note, the exclusion criteria for INR and platelets will have been drawn and evaluated as part of standard of care only, based on the concern for coagulopathy. These are not required to be drawn for study enrollment. All physicians who perform this procedure at Regions Hospital are listed as investigators on this study.

ii. Recruitment

Subjects will be identified based on referral for EBUS TBNA procedure at Regions Hospital by one of the study investigators. Because all physicians who perform the EBUS TBNA procedure at Regions are study investigators, one of the investigators will be aware of every patient referred to have this procedure. Upon becoming aware of a patient referred for this procedure, the study investigator will discuss the procedure with the patient.

iii. Consent

After initial discussion of the procedure (standard of care), the investigator will describe the option to participate in the study as part of the procedure. The consent will be provided and reviewed with the patient/family, explaining the study verbally. The patient undergoing the procedure will provide consent for him- or herself and will be given sufficient time to privately review the consent form and discuss potential involvement in the study with any family members or LAR, as applicable. The investigator will again meet with the patient to address any questions and discuss enrollment. If appropriate, the investigator will obtain consent from the patient and begin the study procedures.

iv. Data Sources:

Data will be obtained before, during, and after the procedure. Demographic data will be obtained prior to the procedure via EMR. Number of passes with each size needle will be recorded in-person following each procedure. Diagnosis yield and adequacy for molecular testing will be obtained following the procedure, from the investigator performing the procedure and from pathology lab analysis as recorded in the EMR and communicated to the investigator per standard practice for this procedure. Complications will be assessed in-person during the procedure and following the procedure via review of the patient's EMR 24± hours after the procedure.

d. Interventions, treatments

The EBUS-TBNA procedure is done with both 19-g and 21-g needles as standard of care. The conduct of the procedure with both needle sizes in a systematic manner with concurrent data collection as described above is specific to the study. This procedure is conducted at Regions Hospital by the listed study investigators. The procedure typically takes between 20 and 90 minutes to complete, during which time the patient is under moderate sedation. During a standard procedure, the physician always performs at least four passes, sometimes more depending on the adequacy of the tissue being obtained. The average is 5.5 passes per lymph node. Participation in the study will likely result in an additional 1 to 2 total passes per patient. The randomization aspect of this study involves randomizing which needle size the physician starts with, with subsequent passes alternating between the two needle sizes. Initial needle size will be randomized using research randomizer. The randomization assignments for each study ID number will be kept in a document accessible by all investigators for use during enrollments. The investigators will not be blinded to the randomization assignment but the subjects will not be informed of which needle size they were assigned to start with.

e. Outcome/endpoint and other variable definitions, and instruments used

Variable Name	Data Source	Purpose	Measurement Scale
Ethnicity	EMR	Covariate	Categorical
Age and gender	EMR	Covariate	Categorical
BMI	EMR	Covariate	Categorical
Primary admission diagnosis	EMR	Covariate	Categorical
Secondary diagnoses	EMR	Covariate	Categorical
Passes with 21-g needle	In-person CRF	Covariate	Continuous
Passes with 19-g needle	In-person CRF	Covariate	Continuous
Total lymph nodes sampled	In-person CRF	Covariate	Continuous
Total sample yield 19-g	In-person CRF	Outcome	Continuous
Total sample yield 21-g	In-person CRF	Outcome	Continuous
Number of adequate samples by rapid onsite evaluation (ROSE)	In-person CRF	Outcome	Continuous

Adequacy for molecular testing for lung cancer	In-person CRF	Outcome	Binary
Follow-up procedures required	EMR	Outcome	Categorical
Complications (hypotension, hypoxia, bleeding, other)	In-person CRF/EMR	Outcome	Categorical
Total time sedated for procedure	In-person CRF/EMR	Covariate	Continuous

f. Statistical analysis plan:

As each needle will be used for every lymph node evaluated, we will assume a paired data structure for analytic strategies. First, demographics and relevant patient factors in the study sample will be summarized using descriptive statistics. Bivariate comparisons (by needle gauge) will be conducted using McNemar tests, paired t-tests, or alternatives appropriate for paired data as dictated by the nature of each variable. If more flexibility is required (e.g., covariates for adjustment, specific correlation structure, random intercepts/slopes for patient clustering), we will specify linear mixed effects regression models to evaluate yield by needle gauge. For secondary aims (complications, etc.) we will employ descriptive analyses – no formal hypotheses will be tested.

g. Power analysis:

Assuming 85 paired samples (50 patients * 1.7 lymph nodes), a one-sided $\alpha=0.05$, and a standard deviation in yield of 10%, we expect 80% power to detect a mean difference of 2.7%. Given our anticipated yields of 83% (21g) and 90% (19g; 7% increase), we expect sufficient power to detect a statistically significant difference in average yield by needle gauge.

h. Strengths and Limitations:

Strengths of the study include:

- All physicians who perform the EBUS-TBNA procedure at Regions Hospital are investigators on this study, therefore we anticipate being able to approach all qualifying patients for enrollment.
- Both needle sizes are currently used as standard of care, based on physician discretion. Use of these needles in the study is not far from the current standard of care and could inform a more standardized methodology for needle size in the future

Limitations of the study include:

- Providers will not be blinded to needle gauge
- Difficult to attribute complications to a single needle gauge, given both will be administered
- As described above, procedural variation depends on physician judgment, which could bias results if judgment is differential with respect to needle gauge and/or yield

5. Setting/Environment/Organizational feasibility

This study will be conducted at Regions Hospital. Subjects will be identified by EBUS providers upon referral for the procedure. A letters of support from Dr. Kealy Ham, Department head of Critical Care Medicine at Regions Hospital, is included with this application. We do not anticipate that the use of both needle sizes during the procedure will significantly affect the resources or personnel utilized during these procedures.

The Critical Care Research Center staff will be responsible for IRB correspondence and data management after collection. Study investigators are very involved with the study and have strong communication with the CCRC staff. The CCRC has conducted numerous studies in collaboration with the Regions Hospital Critical Care Medicine department.

This study fits with the organizational goals at Regions Hospital because it may help to improve patient satisfaction, decrease patient time under anesthesia, and decrease cost of diagnosis for subjects being evaluated with the EBUS TBNA procedure.

Investigator training: All investigators who will be performing the EBUS TBNA procedure are already trained in the conduct of the procedure and are already familiar with the use of both needle sizes. Prior to the start of the study data collection period, the investigators will attend a training meeting during which the specifics of the protocol will be reviewed and any questions discussed. A checklist will be made for use by the investigators during enrollments and investigators will be trained on this checklist and on the data collection instruments. Research staff will remain in close contact with the investigators and have a 24/7 research number where they can contact a research staff member. Investigators will notify CCRC research staff upon completion of enrollments and data collection for each patient. The research staff will collect all enrollment and data collection paperwork from the investigator. Data will be entered on a per-patient basis into an excel spreadsheet on the internal CCRC shared drive. Physical copies of patient study paperwork will be kept in a locked file cabinet in the CCRC, which is a limited access room that requires badge access with specific permission.

6. Risks and Benefits

Risks of EBUS-TBNA procedure

The risks described in this section are related to the EBUS-TBNA procedure, whether done as standard of care or as part of this research study. Bronchoscopy is generally a safe procedure with about 1 in 100 patients reporting a complication. Complications related to the bronchoscopy procedure can be related to sedation for the procedure or directly from the bronchoscope. Complications related to sedation are hypoxia and hypotension, while those related to bronchoscopy are bronchospasm, laryngospasm, nausea, vomiting, bleeding due to scope trauma, abnormal heart rhythm, and fainting. Complications specifically related to EBUS-TBNA are collapse of the lung and bleeding.

An additional risk to subjects is the potential for a breach in patient confidentiality. All study personnel involved in data collection and analysis are trained in GCP, including issues of confidentiality. All study materials will be kept in a locked file cabinet in a badge-access room with limited access and on secure servers, also with limited access. In addition, subjects will be identified in the database by a study number and links to specific identifiers will be kept in a separate secure location. Database files will be maintained on a password protected computer in a secure location and backed up remotely.

Benefits

Subjects may or may not benefit from being in this study. Because of the possibility of getting more tissue with the larger needle, subjects may be able to avoid further testing that may have been necessary if the smaller needle only was used.

We hope the information learned will help other patients undergoing EBUS-TBNA for enlarged lymph nodes in the future.

7. Data Confidentiality and Privacy

   All reports and study materials will be identified only by a subject identification number to maintain subject confidentiality. Tissue samples obtained through the procedure will be identified as per standard procedure for Regions Hospital. These tissue samples will not be retained in any way outside of standard protocol and will not be labeled with the subject's study ID number. A master database linking the patient name & MRN will be maintained on a secure, password protected server in the CCRC. The CCRC uses a secure, electronic system that is currently used at Regions Hospital and is approved by IS&T Security. Any paper case report forms will be stored in locked file cabinets in the CCRC. The CCRC is a locked, protected department with limited badge access for security purposes.

8. Timeline

Submission	April 2018
Review and Approval	April-May 2018
Training	May 2018
Data Collection	June 2018-February 2019
Data Analysis	March-April 2019
Manuscript Preparation and Submission	May-June 2019

9. Dissemination/Sharing Results/Integration and Impact

   We will submit results to an appropriate academic meeting, such as the Society for Critical Care Medicine and plan to publish the results in a journal targeting critical care medicine, i.e. Journal of Critical Care or Critical Care Medicine. We plan to disseminate results both throughout Regions and

the greater organization. This will include departmental and leadership meetings with the departments participating in this research.

10. References

1. Detterbeck, F.C., et al., *Executive Summary: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines.* Chest, 2013. **143**(5 Suppl): p. 7S-37S.
2. Wahidi, M.M., et al., *Technical Aspects of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration: CHEST Guideline and Expert Panel Report.* Chest, 2016. **149**(3): p. 816-35.
3. Hsu, L.H., et al., *Comparison of 19-gauge eXcelon and WANG MW-319 transbronchial aspiration needles.* Thorac Cancer, 2016. **7**(2): p. 264-70.
4. Biswas, A., et al., *Comparison of the yield of 19-G eXcelon core needle to a 21-G EBUS needle during endobronchial ultrasound guided transbronchial needle aspiration of mediastinal lymph nodes for the detection of granulomas in cases of suspected sarcoidosis.* J Thorac Dis, 2017. **9**(9): p. E864-E866.
5. Gnass, M., et al., *Initial Polish experience of Flexible 19 gauge Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration.* Adv Respir Med, 2017. **85**(2): p. 64-68.
6. Herath, S. and W.A. Cooper, *The novel 19G endobronchial USS (EBUS) needle samples processed as tissue "core biopsies" facilitate PD-L1 and other biomarker testing in lung cancer specimens: case report and the view point from the Respiratory Physician and the Pathologist.* Respirol Case Rep, 2017. **5**(6): p. e00271.
7. Trisolini, R., et al., *Endobronchial ultrasound-guided transbronchial needle aspiration with the flexible 19-gauge needle.* Clin Respir J, 2017.
8. Tyan, C., et al., *Flexible 19-Gauge Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration Needle: First Experience.* Respiration, 2017. **94**(1): p. 52-57.
9. Silvestri, G.A., et al., *Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines.* Chest, 2013. **143**(5 Suppl): p. e211S-e250S.