STU00222248

PROTOCOL TITLE: "The SEQUENCE Trial": **S**hould **E**ndobronchial ultrasound **QU**eue b**E**fore or e**N**suing to roboti**C**-assisted bronchoscopy for p**Er**ipheral pulmonary nodule biopsy? A patient randomized control trial assessing the effect of the ordering of robotic-assisted bronchoscopy and linear EBUS during the same anesthesia event on diagnostic yield from peripheral pulmonary nodule biopsy.

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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	None
IND / IDE / HDE #	
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	352 participants across all study sites
Funding Source	Northwestern University
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☐ Yes ☒ No

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FEDERAL FUNDING: N/A

OBJECTIVES:

Robotic-assisted bronchoscopy (RaB) allows for peripheral pulmonary nodule (PPN) biopsy and linear endobronchial ultrasound (EBUS) lymph node staging contemporaneously in the same anesthesia event. The optimal sequence of procedures has not been elucidated, as linear EBUS yielding a diagnosis could obviate the need for RaB, but could also hinder RaB by leading to the development of atelectasis complicating navigation to the peripheral lesion. We propose the following aims for a multi-center, prospective, randomized clinical trial where patients either undergo RaB prior to staging linear EBUS or vice-versa during the same anesthesia event:

- Specific Aim 1: To conduct a non-inferiority randomized trial to assess the effect of having RaB before staging linear EBUS or vice versa on diagnostic yield of peripheral nodule (5-29mm) biopsy.
- Specific Aim 2: To assess potential harms and benefits of the use of intraoperative cone beam CT to assess the incidence of atelectasis in patients randomly assigned to have RaB before linear EBUS staging or vice versa.
- Specific Aim 3: To determine the number of peripheral nodule lung biopsies prevented by performing linear EBUS prior to RaB.

The aims above would be accomplished by the Interventional Pulmonary Outcomes Group (IPOG) with member institutions including high-functioning Ion RaB centers (Northwestern University, Vanderbilt University, Johns Hopkins University, New York University, University of North Carolina, University of California – Davis, University of Michigan, University of California -- San Diego, University of California -- San Francisco, Memorial Sloan Kettering, Ohio State University, Beth Israel Deaconess Medical Center) with myriad experience in performance of high-quality clinical research. This will be opened up to all members of the IPOG community in addition to those listed, so other sites may be added to complete enrollment goal sooner. This study would set the standard for optimizing the sequence of bronchoscopic procedures in patients at risk for early-stage malignancy. It would be a pragmatic assessment of diagnostic yield, assessment of the rate of occult lymph node metastasis, incidence and impact of atelectasis, and safety when patients are undergoing both peripheral nodule biopsy and staging linear EBUS. In addition, the pragmatic nature of the trial would permit adoption almost instantaneously at other institutions.

BACKGROUND:

Robotic-assisted bronchoscopy (RaB) has afforded proceduralists the ability to accurately reach the periphery of the lung for biopsy of pulmonary nodules[1]. This has paved the way for patients to undergo both biopsy of a peripheral nodule and a staging linear endobronchial ultrasound (EBUS) in the same anesthesia event, promoting quicker throughput from discovery of a lesion to guideline-adherent treatment[2]. Further, introduction and mainstream utilization of cone-beam CT (CBCT) has provided the bronchoscopist the ability to refine needle position with tool-in-lesion confirmation[3]. While there are no randomized clinical trials promoting efficacy of RaB and CBCT in comparison with other bronchoscopic methods, in single center retrospective studies, diagnostic yield has consistently proven to be in the 7085% range, superior to prior technologies[4-6].

One of the limitations of utilization of RaB and CBCT is the detrimental effect that atelectasis plays in the bronchoscopy procedure. This can lead to false positive radial EBUS (rEBUS) signals and non-diagnostic procedures[7]. This incidence of atelectasis has been evaluated prospectively, using a protocol featuring

810 cmH2O of PEEP and limiting hyperoxia[8], and results suggest this ventilator strategy does an adequate job preventing intraprocedural lung collapse. However, this study only evaluated incidence of atelectasis and did not elaborate on its impact on diagnostic yield.

Further unknown is the optimal sequence of performance of RaB and a staging linear EBUS in patients with a radiographically normal mediastinum. Starting with either the RaB or Linear EBUS both have their pros and cons. The benefit to performance of a linear EBUS first is the potential to obviate the need for peripheral nodule biopsy by obtaining rapid, on-site pathologic feedback of occult nodal disease, reducing some of the risk of the procedure (i.e. bleeding and pneumothorax).[6] Conversely, the pitfalls to performing linear EBUS first is the possible contribution of atelectasis resultant of the increased time from intubation to peripheral nodule biopsy, blood in the airway causing bronchospasm, and resorption atelectasis from hyperoxia[9]. There are no prospective data evaluating this in a randomized fashion, but one Monte Carlo simulation (with assumption of diagnostic yield from navigational bronchoscopy of 70% when performed first and 60% when performed second) suggested a higher diagnostic yield and less need for repeat procedure in the navigation first group, despite a 10% assumption of occult nodal disease[10].

As outlined in the specific aims above, the overarching goals of this study are to assess in a multicenter, randomized clinical trial performed by members of the Interventional Pulmonary Outcomes Group (IPOG), whether sequence of staging EBUS plays a role in diagnostic yield, incidence of atelectasis, and safety outcomes in patients undergoing RaB.

STUDY ENDPOINTS:

Primary Outcome will be the strict definition of diagnostic yield from the combined EBUS/RaB bronchoscopy procedure.

Major Secondary Objectives:

1) The incidence of atelectasis defined by the following pragmatic scale:
   a. No atelectasis, nodule visualized on CBCT
   b. Some atelectasis, but nodule still visualized on CBCT
   c. Atelectasis preventing nodule biopsy
2) Next Generation Sequencing (NGS) sufficiency from EBUS and peripheral nodule biopsy
3) PPN biopsies obviated by starting with EBUS first
4) Safety outcomes (bleeding, pneumothorax)
5) Procedural time
6) Impact of patient factors (BMI, Pulmonary Function Tests, etc) on diagnostic yield **STUDY**

INTERVENTION(S) / INVESTIGATIONAL AGENT(S): N/A

PROCEDURES INVOLVED:

We propose a multicenter (Vanderbilt University, Johns Hopkins University, New York University, University of North Carolina, University of California – Davis, University of Michigan, University of California -- San Diego, University of California -- San Francisco, Memorial Sloan Kettering, Ohio State University, Beth Israel Deaconess Medical Center), pathologist-blinded (though not cytopathology onsite technician or physician), 1:1 randomized clinical trial evaluating the effect of performance of RaB then

staging linear EBUS versus staging linear EBUS first, followed by RaB. Patients evaluated by the interventional pulmonary service at their respective institutions will be enrolled if they are scheduled to undergo a peripheral pulmonary nodule biopsy, do not have significant (≥1.0cm) mediastinal or hilar lymphadenopathy, and do not have FDG-PET/CT-avid lymphadenopathy.

All patients located within outpatient pulmonary clinics or pre-operative holding areas planning to undergo a bronchoscopic biopsy of a peripheral pulmonary nodule accessible by RaB and staging linear EBUS bronchoscopy for initial diagnosis and possible staging will be eligible for participation. Patients will then be randomized in a 1:1 fashion to receive RaB 1st (R1) or linear EBUS 1st (E1).

All patients will be consented and subsequently intubated in the usual fashion at the institution. Patients will be ventilated with the following parameters:

- PEEP of 8-10 cmH2O.
- SpO2 maintained between 92-99% with titration to prevent resorptive atelectasis.

Then, the proceduralist will randomize the patient to either R1 or E1 (below).

R1: The proceduralist will first perform an Ion robotic-assisted bronchoscopy in the usual fashion with calibration to the airway, navigation to the lesion, and biopsy using the bronchoscopists' tool of choice (typically needle of varying gauge followed by either forceps or 1.1 mm cryoprobe). Rapid on-site evaluation (ROSE) from cytopathology can be utilized in these cases to confirm diagnoses, though is not mandatory. After completion, the patient will then undergo a staging linear EBUS to assess for occult nodal disease and providers will biopsy any enlarged (>5mm) lymph nodes.

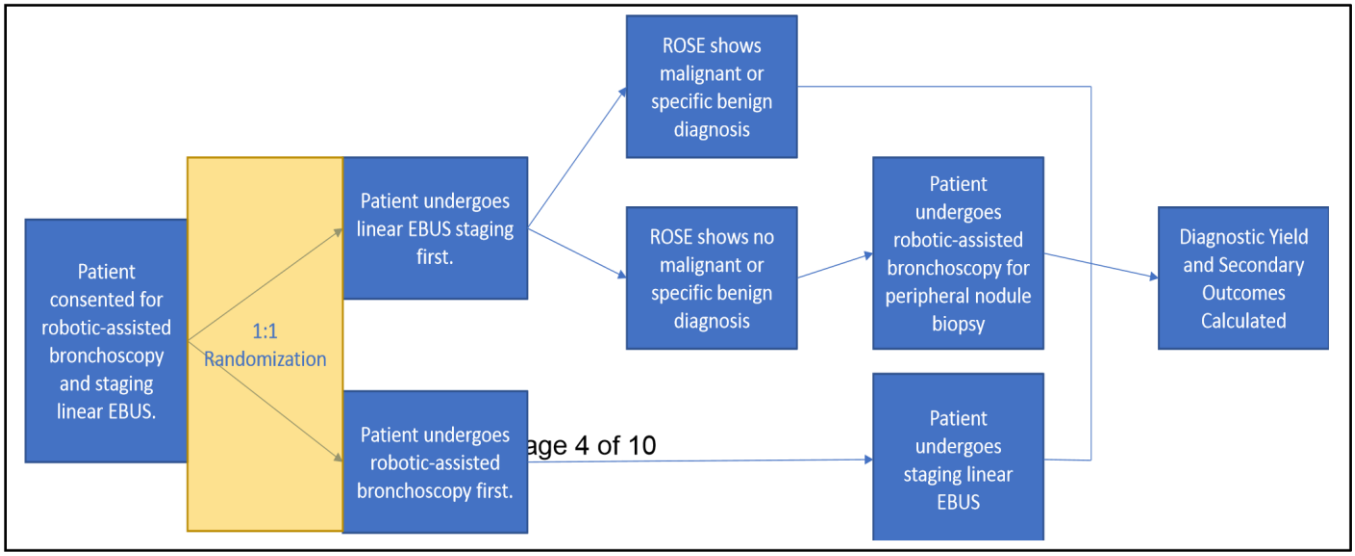
E1: The proceduralist will first perform a linear EBUS procedure to assess for occult nodal disease and lymph node biopsies will be taken at the discretion of the proceduralist. All lymph nodes >5mm will be biopsied based on current guidelines. The proceduralist will then move on to perform peripheral biopsy via use of RaB.

All patients: During the RaB procedure, CBCT will be utilized to assist the bronchoscopist with tool-inlesion confirmation when navigating to and biopsying the PPN. Atelectasis will be evaluated based on the following scale 1) no evidence of atelectasis, 2) atelectasis as determined by the bronchoscopist, but not obscuring the lesion and able to proceed with nodule biopsy, or 3) atelectasis preventing biopsy of the nodule. This score will then be recorded.

Upon completion of the procedure, diagnostic yield will be defined by strict criteria, and only data from the initial procedure and not follow-up will be taken into account as per the recently published American Thoracic Society consensus statement[11]. A diagnostic procedure will be defined as a malignancy or a specific benign diagnosis (i.e. granuloma or organizing pneumonia). Atypical cells, nonspecific chronic inflammation, and other diagnoses without actionable information will be considered non-diagnostic. At 30-days follow up, sufficiency for NGS, need for an additional diagnostic procedure, and assessment of culture data will be undertaken by a member of the study team.

Patients with a non-diagnostic PPN biopsy will be followed for one-year assessing for requirement of an additional diagnostic procedure or radiographic stability. They will not require another study visit. This will be performed via chart review by the research team.

Data will be collected and stored in a de-identified manner in a redcap database hosted by Northwestern University.



The research team will also collect demographic data from the EMR, procedural characteristics, and pathologic outcomes. Collected data will include lymph node characteristics, procedural characteristics including time at each lymph node station, pathologic diagnosis, and adverse events as follows:

- Demographics: Age, sex, race/ethnicity
- Dates: Age (though not specific DOB), date of procedure.
- Nodule characteristics: Size, spiculation, location in the lung.
- Lymph Node characteristics: Size of the lymph node and other characteristics may be documented in the REDCap form.
- Procedural Characteristics: Ventilation parameters, time of procedure, number of CBCT spins, radiation from the CBCT (mGy and time).
- Final Pathologic Diagnosis: Strict reporting of diagnostic yield (malignant or specific benign diagnoses of granuloma or organizing pneumonia will be counted as diagnostic).
- One Year Follow Up: Will occur for patients with a non-diagnostic initial procedure to discern if another procedure made the diagnosis, or if the nodule displayed benign characteristics on imaging follow up .
- Adverse Events: Any AEs that occur during the procedure will be recorded and assessed by the PI or Sub-Is regarding their relationship to the study procedures.

DATA AND SPECIMEN BANKING

Data will be stored in a secure REDCap database hosted on the Northwestern website with password protection only accessible to study personnel. All identifiers (Patient Name, DOB, MRN, contact information) will be stored in StudyTracker, aside from dates (date of consent, date of procedure). Once the study is closed, identifiers stored in StudyTracker will no longer be accessed, ensuring that the data retained is a limited dataset (with no identifiers included aside from dates as noted above). Data sharing agreements will be put into place for outside institutions and only the limited dataset will be shared between the groups.

SHARING RESULTS WITH PARTICIPANTS

Results from the study will not be shared with participants.

STUDY TIMELINES

Patients will be enrolled before or on the day of their standard of care RaB and linear EBUS procedure and this will be the only study visit. Patients' data will then be evaluated at the 30-day mark to obtain strict definition of diagnostic yield. Patients with a non-diagnostic bronchoscopy will then fall into the 1 year follow up category and the study team will reassess their data at one year, without another required visit from the subject.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria: Any adult patient undergoing RaB with CBCT for a peripheral pulmonary lesion (829mm) that will also have a staging linear EBUS performed in the same anesthesia event.

Exclusion Criteria:

1) Patient is known to be less than 18 years old, pregnant, or a prisoner.
2) Proceduralist deems lesion is not safe for biopsy.
3) Patient has evidence of PET-Avid mediastinal/hilar adenopathy that could obviate the need for peripheral pulmonary nodule biopsy.
4) Patient has evidence of enlarged hilar or mediastinal lymph nodes (>1.0cm) on non-PET CT of the chest.

5) Peripheral pulmonary nodule is ≥30mm in diameter

VULNERABLE POPULATIONS

Will not be recruited for this study.

PARTICIPANT POPULATION(S) AND POWER CALCULATION

Non-inferiority

This study will be powered to detect the equivalence of the two procedural sequences, R1 and E1, with respect to the primary outcome, diagnostic yield. Preliminary data suggest a diagnostic yield of 75% within the E1 intervention arm. Sample size calculations assumed power of 80% with a 5% type-1 error rate from a non-inferiority test (limit = 2.5%) for the difference between two proportions (one-sided ztest with pooled variance) (TABLE).

TABLE. Sample size needed to detect equivalence between study arms from a one-sided z-test with pooled variance of two proportions assuming 80% power and alpha = 0.05

	Diagnostic yield in E1 arm = 75%			
Observed diagnostic yield in R1 arm	82%	83%	84%	85%
Total sample size	462	372	304	252
Total sample size accounting for 5% drop out	487	392	320	266
Enrollment per study arm	244	196	160	133
	Diagnostic yield in E1 arm = 80%			
Observed diagnostic yield in R1 arm	87%	88%	89%	90%
Total sample size	378	302	244	202
Total sample size accounting for 5% drop out	398	318	257	192
Enrollment per study arm	199	159	129	96

Using the sample size calculations of an approximation of 75-80% diagnostic yield in E1 and an observed difference in diagnostic yield of 8-9% (84% or 88%, respectively) for the R1 arm with a 5% dropout rate (due to patients being consented and subsequently not undergoing a biopsy), the sample size required in each group would be 176 participants for a total of 352 participants across all study sites.

<u>Statistical analysis</u>

The primary outcome, diagnostic yield, is binary. Statistical equivalence tests based on a normal approximation to a binomial distribution will be used to determine whether the prevalence of the outcome in the two intervention groups are the same. Exploratory subgroup analyses will be conducted in the following groups: site of nodule (upper lobe or not) and nodule size (8-1.5mm or 1.6-2.9mm). Secondary outcomes will be analyzed via generalized linear models, with link functions chosen based on the outcome type (logit for binary outcomes, identity for continuous outcomes).

RECRUITMENT METHODS

Patients who are scheduled for a standard of care RaB with linear EBUS at Northwestern or one of the other participating institutions will be screened by the study team. All patients undergoing a RaB with linear EBUS for a peripheral nodule biopsy who meet the inclusion criteria may be approached for participation. Patients may be approached before or on the day of the planned standard of care procedure by one of the study team members to provide informed consent. Patients may be approached in person during their standard of care clinic or bronchoscopy visit, or one of the study team members may contact the patient by phone and/or email. If the patient is contacted by phone or email, and are interested in hearing more about the study, the study team will send the consent form by email to the patient and arrange a time to discuss the study over the phone or video call. If the patient agrees to participate, the study team will send the consent form for signature via DocuSign and will send a final signed copy by email back to the study participant. The study team will document that the consent process took place remotely in StudyTracker.

Any patients not wishing to participate in the study will still have the standard of care procedure completed at the assigned time.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES None

WITHDRAWAL OF PARTICIPANTS

Subjects who provide informed consent but are determined to be ineligible will be considered screen failures. The reason for screen failure will be documented and the procedure will continue as per standard of care.

RISKS TO PARTICIPANTS

There is no expected physical risk related to whether RaB or linear EBUS is performed first. There is equipoise as to the preferred method and each are practiced throughout the world based on provider preferences. There are no studies to date to suggest superior efficacy or higher risk with either method.

There is the risk of loss of confidentiality of health information. To minimize this risk, all coded clinical data collected and used as part of this project will be stored in a secure REDCap database or on a password-protected spreadsheet stored securely by the PI/Co-Is. Only elements of dates will be included in the REDCap database (date of consent, date of procedure, etc.). The key linking the code to identifying information (name, DOB, MRN, contact information) will be stored securely in StudyTracker.

POTENTIAL BENEFITS TO PARTICIPANTS

There is no direct benefit to participants. This research may help us determine the optimal way to perform this procedure, potentially saving environmental costs or time under anesthesia in the future.

DATA MANAGEMENT AND CONFIDENTIALITY

To protect confidentiality, all data will be coded with a study code. Data will be password-protected and stored securely by the PI/Co-Is on their computers, on FSMResFILES or NM SharePoint, and on a REDCap database. Coded data will be stored on REDCap until at least 3 years after study closure. Coded data may be shared with other investigators conducting IRB-approved projects that reference the use of these data, upon permission from the PI. Codes will be linked to identifying information (name, DOB, MRN, contact information) via StudyTracker.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

Consenting done in person will be conducted in a private location at the clinic or bronchoscopy suite. All participants will be informed that participation in this study is optional and will not affect their medical care. All personal health information will be coded at the time of collection. Only the authorized research personnel for this study will have access to the key linking the code to the participant's name and other identifying information. Identifying information may be used to obtain health information from the electronic medical record (Epic) for this research study. The key to the code will be kept in confidential files with standard security precautions and will never leave Northwestern University.

ECONOMIC BURDEN TO PARTICIPANTS

There are no costs to the participant for being in this study. The bronchoscopy procedure is performed for standard of care and will be billed to the patient and/or to the patient's insurance company in the usual way. Insurance dictates procedural cost and reimbursement and is not based on the equipment used or order in which it is performed.

CONSENT PROCESS

Written informed consent will be obtained from each participant by the PI, Co-Is, or their study coordinators, either at the time of an in-person visit or remotely. If consent if obtained remotely, the research coordinator will contact the patient by phone or email to arrange a time to review the informed consent form (ICF). The research coordinator will send the ICF by email ahead of time to the patient and will arrange to speak with the participant via phone or video call for the consent review. If the patient is interested in participating, the coordinator will send the ICF for signature via DocuSign and will send a final copy by email back to the participant. The coordinator will also document that the ICF process took place virtually in StudyTracker. The physicians and study coordinators will verbally explain the study in detail and ensure that any questions are answered before prospective participants sign the consent form. They will reinforce that participation in the study is voluntary and they can withdraw their consent at any time.

Consent may be obtained on the day of the procedure. Consent will not follow any stressful situation (ie, patient being informed he/she may have cancer) and will not be conducted if the patient has received any mind-altering medications or anesthesia. Patients will be assessed for their capacity to consent by the ability to show comprehension of the research, ask appropriate questions, and appear properly oriented. A signed copy of the consent form will be offered to participants.

NON-ENGLISH SPEAKING PARTICIPANTS

We will utilize the short form consent with the assistance of a translator for non-English speaking participants. Once the same short form has been used for two participants or the English main ICF has undergone revision, we will translate the main ICF.

WAIVER OR ALTERATION OF CONSENT PROCESS: N/A

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

A HIPAA Authorization will be obtained as part of the consent form for the use of Protected Health Information (PHI). Health information that we may collect and use for this research includes:

- Names
- Dates: All elements of dates directly related to an individual, including birth date, date of procedure, etc.
- Contact information (Address, telephone number, email address)
- Medical record number
- Demographic information (Age, sex, race/ethnicity)
- Information related to the EBUS bronchoscopy (such as procedural characteristics including time at each lymph node station)
- Bronchoscopy results (such as lymph node characteristics, pathologic diagnosis)
- One-year follow up of clinical data for persons undergoing non-diagnostic initial procedure (radiology results, other biopsy results)

WAIVER OF HIPAA AUTHORIZATION: N/A

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

All physicians performing the EBUS procedures for this research are study investigators. The PI and Co-Is have extensive experience in clinical research and the Division of Pulmonary and Critical Care Medicine has experienced research managers and coordinators who will assist with this study, including consenting patients, creating a REDCap database for data collection, and obtaining and entering clinical data.

The PI/Co-Is perform 5-7 RaB procedures per week, so have sufficient volume of patients to conduct this study.

MULTI-SITE RESEARCH: This research will be performed at Northwestern University as the host site, with Vanderbilt University, Johns Hopkins University, New York University, University of North Carolina, University of California – Davis, University of Michigan, University of California -- San Diego, University of California -- San Francisco, Memorial Sloan Kettering, Ohio State University, Beth Israel Deaconess Medical Center potentially contributing data from their patients. This will be opened up to all members of the IPOG community, so other sites may be added to complete enrollment goal sooner. Although this is a multi-site study, Northwestern University IRB will serve as the IRB of record only for the Northwestern study site. All other sites will obtain local IRB approval for this study.

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