

CrYobiopsy with Radial UltraSound
Guidance (CYRUS) - a Randomized
Controlled Study

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General Study Information

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Title: CrYobiopsy with Radial UltraSound Guidance (CYRUS) - a Randomized Controlled Study

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Purpose

Hypothesis

Transbronchial cryobiopsy carries a higher chance of establishing pathological diagnosis in diffuse parenchymal lung disease (DPLD) than traditional transbronchial forceps guided biopsy¹. It is a novel technique capable of obtaining large, high-quality samples of lung tissue in a minimally invasive manner. This procedure may decrease the need for surgical lung biopsy in 75% of cases². However, there is an increased risk of pneumothorax and airway bleeding compared to traditional transbronchial forceps guided biopsy³.

Several strategies are used by practitioners of this technique to mitigate the risks of significant bleeding and pneumothorax. These include prophylactic placement of an endobronchial blocker, the use of fluoroscopy guidance, instillation of cold saline to promote vasoconstriction, and establishment of a secure airway with endotracheal tube placement or rigid bronchoscopy⁴.

Vanderbilt University Medical Center is one of the most active centers in terms of cryobiopsies performed as part of the diagnostic workup of DPLD. Currently all transbronchial cryobiopsies here are performed under fluoroscopic guidance, with endotracheal tube intubation and endobronchial blocker placement⁵. Despite these precautions, post biopsy bleeding complications occur and can substantially lengthen the duration of the procedure and occasionally expose patients to procedural complications.

Radial ultrasound has been well utilized to define anatomy of peripheral lung and localization of peripheral pulmonary nodules⁶. We postulate that using radial ultrasound to identify peribronchial lung parenchyma with low vascularity will mitigate the risk of hemorrhage during peripheral lung cryobiopsy in patients with DPLD and hence improve patient safety.

Aims and Objectives

To study the impact of radial probe ultrasound guidance for localization of areas of low vascularity to decrease bleeding complications after cryobiopsies.

Expected Outcomes

We anticipate that using radial ultrasound guidance during transbronchial cryobiopsy will result in decreased bleeding. This will be measured by time spent to achieve hemostasis after each biopsy (primary endpoint). Other endpoints will include grade of bleeding after each biopsy, use of additional modalities to control bleeding, size of biopsy, histologic evidence of vascular structures and histologic diagnosis (secondary endpoints).

Background

Diffuse parenchymal lung diseases comprise a group of noninfectious, non-neoplastic lung diseases, each characterized by varying degrees of inflammation or fibrosis of the parenchyma of both lungs. The differentiation of these disorders may require biopsy material, particularly in patients with atypical clinical or radiological presentations. Cryobiopsies offer specialists the advantage of being able to collect much larger specimens than can be collected with forceps biopsy, while preserving the underlying lung architecture (no crush artifact). The biggest disadvantage of cryobiopsy is a higher risk of procedural bleeding and, to a lesser extent, pneumothorax than conventional transbronchial lung biopsies.

Existing cryobiopsy literature is significantly limited by lack of procedure standardization, variable diagnostic endpoints and non-uniform grading of complications. Surgical lung biopsy, currently the gold standard for histological diagnosis of DPLD, is associated with significant morbidity and mortality. The rate of in-hospital mortality following SLB for DPLD was recently found to be 1.7% in a large dataset, with a complication rate of 30% (including post-operative pneumothorax, pneumonia, respiratory failure)⁷. Mortality was slightly lower at 1.5% for elective operations but markedly higher at 16% for operations labeled “*non-elective*,” presumably performed in the setting of acute disease exacerbations. Clearly, less invasive strategies, such as cryobiopsy, are urgently needed.

Recent studies demonstrate that there might be a trend toward more bleeding complications with transbronchial cryobiopsies⁸. The increased risk of bleeding is due to the larger biopsies thus obtained, and the necessity to retrieve bronchoscope and cryoprobe en-bloc as biopsies are too large to be pulled through the working channel of the bronchoscope, preventing the proceduralist from keeping the bronchoscope wedged in the biopsied segment allowing bleeding tamponade.⁹ Accordingly, most proceduralists perform cryobiopsy with prophylactic placement of bronchial blocker positioned proximal to the selected lobe to occlude the segmental airway after biopsy. While this technique has essentially eliminated the risk of life-threatening bleeding after cryobiopsies, significant bleeding complications persist and can occasionally substantially lengthen the duration of the procedure, leading to premature termination and potentially quantitatively inadequate biopsy acquisition.

Conceptually it seems that the ability to select a less vascular area for a somewhat larger cryobiopsy may result in decreased risk of hemorrhage and/or reduction in bleeding severity. Average peripheral cryobiopsy size varies significantly and may be dependent on freezing time and cryoprobe size¹⁰⁻¹². Increase in resource utilization due to the use of radial ultrasound could be offset by a decrease in complication rate, decreased procedural time and potentially decreased endobronchial blocker need. This use of radial probe ultrasound use

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has not been widely reported in literature except for a recent single center retrospective review of 10 patients undergoing transbronchial cryobiopsies for ILD (Berim, 2017). Six of these patients underwent vascular localization with radial probe endobronchial localization with trends towards less bleeding.

The purported benefit of radial ultrasound-guided transbronchial cryobiopsy is the avoidance of excessive bleeding, which has been associated with this procedure. With the systematic use of a prophylactic bronchial blocker, an ideal endpoint for this pilot study would be the time spent obtaining each biopsy. We propose to study in a prospective, double-blind, randomized controlled fashion, the efficacy of radial endobronchial ultrasound (in combination with fluoroscopy) guided transbronchial cryobiopsy as compared to conventional fluoroscopy guided cryobiopsy in reducing time needed to achieve hemostasis (primary endpoint) and need for additional modalities to control bleeding and size of biopsies obtained (secondary endpoints).

Subject Information

All consecutive patients referred to outpatient interventional pulmonology for diagnostic transbronchial cryobiopsy will be screened for study inclusion.

Target accrual

Based on our power calculation, we plan for 40 total biopsies to be randomized 1:1 (block of 4) to the intervention (radial probe ultrasound + fluoroscopy guidance) or the control group (fluoroscopy guidance only).

Inclusion criteria:

1. Referral to interventional pulmonary services for diagnostic transbronchial cryobiopsy for diffuse parenchymal lung disease.
2. Transbronchial cryobiopsy is determined to be appropriately indicated as determined by consulting interventional pulmonologist.
3. Age > 18 years

Exclusion criteria:

1. Inability to provide informed consent
2. Study subject has any condition that interferes with safe completion of the study including:
 - a. Coagulopathy, with criteria left at the discretion of the operator
 - b. Respiratory insufficiency with DLCO < 30% or baseline requirements of oxygen > 2 liters
 - c. Hemodynamic instability with systolic blood pressure < 90 mmHg or heart rate > 120 beats/min, unless deemed to be stable with these values by the attending physicians
3. Patients representing vulnerable populations (prisoners, pregnant women, etc.)

Enrollment

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The screening and enrollment of subjects will be done by a study coordinator or an investigator who is a member of the research team. The study coordinator will be responsible for ensuring and reporting subject screening for study eligibility. Once the investigator has determined the subject's eligibility for the study, the background of the proposed study and the benefits and risks of the study and procedures will be explained to the subject as a part of consenting process. After consenting, subjects will be considered enrolled if they meet all the inclusion criteria and none of the exclusion criteria. Subjects who fail to meet any of the entry criteria will be excluded from the study and considered a screen failure.

Informed Consent

The informed consent will be obtained by the study coordinator or one of the investigators of the study with clear description of the purpose and procedures of the study, the implications for enrolled patients in terms of clinical care whether they decide to participate in the study or not, the potential risks and benefits of the study. It will be made clear to participants that they will be a liberty to withdraw from the study at any point or decline participation outright without impacting their level of clinical care. Oral and written consent will be obtained, with the signed informed consent archived in the research department of the Division of Pulmonary & Critical Care at Vanderbilt University, with a copy kept in the patient's electronic medical records. The patient will be furnished with a copy of the signed study documents for his or her personal records.

Study Design

Study Procedures

Randomization Process and Subject blinding

All patients undergoing peripheral lung cryobiopsy for diffuse parenchymal lung disease will be offered participation in the study per the inclusion/exclusion criteria. The primary bronchoscopist will select appropriate general areas of lung parenchyma for cryobiopsy per review of available computerized tomographic scan of the chest and per standard clinical protocol. Procedures will be performed by an attending interventional pulmonologist or interventional pulmonary fellow under direct supervision in a dedicated bronchoscopy operating room with standard monitoring at least 7 days after last antiplatelet or anticoagulant medication use. All procedures, except for the radial ultrasound use which is a non-invasive imaging tool, are standard of care and are not modified for the purpose of this procedure.

1. After topical anesthesia of the oropharynx, vocal cords, and upper trachea with lidocaine each subject will be intubated with an 8.5 mm wire reinforced endotracheal tube (Smiths Medical, St Paul, MN) advanced over flexible bronchoscope (Olympus XT180 or BF-1TH190; Olympus America Inc., Center Valley, PA).
2. Oxygen will be delivered per tube but the cuff will not be inflated unless indicated to assist ventilation.
3. A procedural pause/time out will be performed, during which patient identity, type of the procedure, and presence of signed consent documents will be confirmed in the presence of the patient, the proceduralist, and a nurse per standard VUMC protocol.

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4. A certified registered nurse anesthetist will provide intravenous deep sedation and adequate spontaneous respiratory effort will be maintained as much as possible. Paralytics will be used only if adequate sedation and spontaneous assisted ventilation cannot be safely co-maintained.
5. Areas of significant abnormality on pre-procedure computed tomography scan will be targeted. The lower lobes will be preferentially biopsied, attempts will be made to take each biopsy was taken from a different segment. As per standard of care, 4 biopsies will be obtained per patient, all from different segments and at least from two different lobes. Only one lung will be biopsied.
6. Real-time fluoroscopy will be used in all cases to guide the radial probe ultrasound and/or cryobiopsy probe placement.
7. In **the control group**,
 - a. A 1.9 mm diameter carbon dioxide-cooled cryoprobe measuring 90 cm in length (ERBE Elektromedizin GmbH, Tübingen, Germany) will be advanced until resistance is felt or the probe is seen fluoroscopically to reach the pleura.
 - b. Secondary bronchoscopist will be called into the room after prompted so by study coordinator.
 - c. After pulling back 1.5 to 2 cm, the cryoprobe will be activated for 5 seconds before cryoprobe and bronchoscope are pulled out of the airway en bloc.
 - d. A prophylactic bronchial blockade using a 7 Fr endobronchial blocker (Arndt; Cook Medical, Bloomington, IN) will be inflated by the bedside assistant while the bronchoscope is out of the airway after each biopsy.
8. In **the intervention group**,
 - a) Radial ultrasound probe (Olympus UMS20-17S) will be passed under fluoroscopic guidance into the subsegmental branches of the target lobe and will be advanced until resistance is felt or the probe is seen fluoroscopically to reach the pleura.
 - b) After pulling back 1.5 to 2 cm radial probe will be positioned 1 to 2 cm away from pleural surface and activated.
 - c) Absence of ultrasonographically identifiable vasculature will be confirmed. Ultrasound probe will then be slowly withdrawn until pulmonary vasculature is noted.
 - d) If at least 1 cm area with absence of sonographically identifiable vasculature cannot be obtained, alternative airway will be selected and process repeated.
 - e) Once the target area for biopsy was established, a 1.9-mm cryoprobe (ERBE 20416-033) will be passed through the bronchoscope into the target area and positioned at the same position as the radial probe.
 - f) Secondary bronchoscopist will be called into the room after prompted so by study coordinator. Radial ultrasound image will be erased before his arrival to maintain blinding.
 - g) A 5 seconds cryoprobe activation will performed by calling out freeze time by the primary bronchoscopist.
 - h) Bronchoscope and cryoprobe will then removed en bloc.
 - i) A prophylactic bronchial blockade using a 7 Fr endobronchial blocker (Arndt; Cook Medical, Bloomington, IN) will be inflated by the bedside assistant while the bronchoscope is out of the airway after each biopsy.

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9. At the time of removal of the bronchoscope and cryoprobe en bloc the study coordinator will start the stop watch to start recording time to achieve hemostasis.
10. The cryobiopsy will be submerged in room temperature saline to rapidly thaw and release the tissue, allowing the cryoprobe to be removed.
11. Bronchoscope will be switched to secondary bronchoscopist
12. Bronchoscope will be quickly reintroduced into the airway to confirm inflation and position of the bronchial blocker occluding the biopsied airway.
13. At the discretion of the secondary bronchoscopist, strategies to achieve hemostasis will be carried out including iced saline, suction, tamponade and re-inflation of blocker, patient repositioning etc. A rigid bronchoscope will be immediately available to manage complications as per standard of care.
14. After satisfactory hemostasis is obtained and it is considered safe to proceed with next cryobiopsy, the secondary bronchoscopist (blinded to biopsy technique) states out loud “Ready for new biopsy”. This way the study coordinator will be prompted to stop the stop watch, time recorded and scope will be handed back to primary bronchoscopist and secondary bronchoscopist will exit the operating room.
15. At the discretion of the operator the process will be repeated in different location in the same lobe to achieve up to 4 biopsies.

Process of Randomization and Blinding:

1: 1 randomization will be performed with random permuted blocks of 4 to randomize allocation between intervention and control arms.

Each biopsy will be randomly allocated into intervention (radial probe ultrasound and fluoroscopy guided) and control (fluoroscopy-guided) groups by opening an opaque study envelope just prior to starting the procedure containing group assignment.

Patients and Blinding Process

Patients will be informed that as a part of the trial we plan to obtain 4 cryobiopsies(2 with radial probe assistance and 2 without). This is also the same as average number of biopsies we obtain in patients who are not a part of this trial as a standard of care. The criteria to stop the procedure earlier if needed are the same as those for patients not on this trial.

Patient will receive cryobiopsy by both intervention and control modalities unless the procedure has to be terminated prematurely, as standard of care.

Proceduralists and Blinding Process:

Three proceduralists will be involved in the procedure. Primary bronchoscopist will perform the localization of the biopsy spot as described above, after the biopsy is determined to be in the control or the intervention group. He/she will also then perform the cryobiopsy per protocol. A bedside assistant will be assisting in managing the endobronchial blocker at all times. He/she will inflate the endobronchial blocker balloon as soon as the bronchoscope is removed en-bloc with the cryoprobe.

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Secondary bronchoscopist will be stationed outside the bronchoscopy OR during this initial part of the procedure (localization and obtaining cryobiopsy). He will then be prompted to enter the room by research coordinator and take control of the bronchoscope. Secondary bronchoscopist, will be blinded to the use or non-use of radial probe ultrasound for that particular biopsy. Research coordinator will be present at all times and will coordinate the switching process between the proceduralists. Attention will be paid that the personnel present in the room does not mention the use or non-use radial ultrasound probe to the secondary bronchoscopist. The reference image of the radial USG determining the biopsy location on monitors will be erased before secondary bronchoscopist enters the room to maintain blinding.

Recording of Outcomes

The time to achieve hemostasis will be recorded with help of a stop watch by the study coordinator in the operating room. Stop watch will be turned on from the time bronchoscope and the cryoprobe are removed en bloc after obtaining cryobiopsy and turned off at the time it is determined to be safe to proceed to the next cryobiopsy (secondary bronchoscopist, blinded to biopsy technique states out loud "Ready for new biopsy").

The procedure can be terminated prematurely, as standard of care, if any the following occur:

1. Significant bleeding precluding obtaining further cryobiopsy
2. Hemodynamic instability
3. Respiratory instability
4. At the primary bronchoscopist's discretion

Post-procedure PA/lateral chest radiograph will be performed to assess for development of pneumothorax as per standard of care.

Outcomes:

Primary endpoint:

1. Time to achieve hemostasis after obtaining cryobiopsy:

This is defined as time from when the bronchoscope and cryoprobe are removed en bloc after obtaining the cryobiopsy to the time when it is determined to be safe to proceed to next cryobiopsy("Ready for next biopsy").

This study is a randomized controlled trial designed to test the hypothesis that the time to achieve hemostasis in cryobiopsy performed with additional radial probe guidance will be less than that of cryobiopsy performed without radial probe ultrasound localization of presence of vasculature. The estimated minimal clinically important difference is 60 seconds.

Secondary endpoints:

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1. Grade of bleeding
2. Additional interventions used to manage bleeding – cold saline, patient positioning, rigid bronchoscopy, embolization, etc.

All biopsies are currently being independently analyzed as part of our ongoing QI project COOL_HUES (IRB#161260). This will allow us to collect following secondary end points:

3. Biopsy specimen quality
4. Biopsy size

Variables recorded:

- Past medical history
- Demographic data
- Smoking history
- Current medications
- Laboratory data (complete blood count, electrolytes, creatinine, coagulation profile if available)

Statistical methodology

Power calculation

The primary goal of this study is to compare the performing cryobiopsy with and without use of radial ultrasound. The primary endpoint of the study is time needed for each biopsy. Without the use of radial ultrasound, we observed time needed for one biopsy (min) of 2 ± 1 (mean \pm SD). We usually perform 4 biopsies in each patient in practice. Thus, we plan to randomize the biopsies into convention (without use of radial ultrasound) and intervention arms (with use of radial ultrasound) within each patient. Sample size is calculated from paired t-test. Compared to the convention arm, a sample size of 10 patients achieves 80% power to detect 1 minute decrease in the intervention arms with type 1 error of 0.05.

Statistical analysis plan

Descriptive statistics including means, standard deviations, and ranges for continuous parameters, as well as percentages and frequencies for categorical parameters will be presented. Investigations for outliers and assumptions for statistical analysis, e.g., normality and homoscedasticity will be made. If necessary, data will be transformed using Box-Cox power transformation. Comparisons between groups, i.e. intervention vs control, will be made using either the t-test or Wilcoxon Rank Sum test for continuous variables time to achieve hemostasis, size of biopsy and Chi-square test for categorical variables (such as incidences of pneumothorax, grade of bleeding)

Safety

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We do not expect additional safety concerns from this protocol over those incurred during conventional transbronchial cryobiopsy explained to all patients undergoing cryobiopsy as part of the clinical informed consent. These risks, inherent in the procedure itself, include pneumothorax, bleeding or respiratory failure. We do not expect that use of radial ultrasound for additional localization will result in an increased risk for the patient.

Adverse event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment.

The procedures being performed, transbronchial cryobiopsy with or without radial probe ultrasound guidance are standard of care/routine procedures. There are no research procedures post-treatment, and patients will not be followed for study purposes. Only adverse events related to research procedures (the consent process, HIPAA compliance, etc.) will be collected. PI will be monitoring all data daily, ensure that PHI is protected and review all AEs and SAEs and report all SAEs within 5 business days to the IRB. Serious adverse events will be recorded as part of the study.

Serious adverse event (SAE)

A serious adverse event (SAE) 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.

If a massive bleed is encountered after cryobiopsy, the management is initiated with immediate attempt to occlude the bleeding airway. Dedicated endobronchial balloon or the bronchoscope itself can be used for this purpose. The patient will be then rotated to a lateral position with bleeding side down. Instillation of ice-cold saline can help in achievement of hemostasis by causing cold-induced vascular constriction. Selective intubation of nonbleeding lung can be performed in persistent severe bleeding. Patient can be referred to interventional radiology for localization and embolization of the bleeding vessel. Fatality from such hemorrhage is extremely rare, however, has been described previously³.

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General Instructions for Reporting Serious Adverse Events

The Institutional Review Board be notified of all SAEs, within 5 business days after the treating institution becomes aware of the event. Only AEs related to research procedures will be reported to the IRB.

Data and Safety Monitoring

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the treating investigator or site staff will be responsible for detecting, documenting, and report AEs and SAEs, as detailed in the protocol. If any problem appropriate for review is identified related to the conduct of this research, the Allergy, Pulmonary and Critical Care Medicine (APCCM) Data Safety and Monitoring Committee (DSMC) will be formally asked to review the study and the situation that required DSMC intervention.

Personnel from the APCCM Division will monitor the trial and may periodically visit the investigative site to assure proper conduct of the trial and proper collection of the data. These monitoring visits may occur remotely or on-site. The investigator will allow the monitor to review all source documents used in the preparation of the case reports.

Data Handling and Record Keeping

Electronic case report forms (eCRF) are required and will be completed for each included participant. The completed dataset will not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from Vanderbilt, per the clinical trial agreement and patient signed informed consent.

To enable evaluations and/or audits from health authorities and Vanderbilt, the 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 drug disposition. The records should be retained by the investigator in compliance with regulations.

During data entry, range and missing data checks will be automated through REDCap (when appropriate and able). The checks to be performed will be documented in the Data Monitoring Plan for the study. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

General design of the study

See CONSOR diagram / flow chart **attached**.

Data Collection:

Data will be collected using a centralized electronic case report form called REDCap, currently locatable at: <https://redcap.vanderbilt.edu/>. REDCap is a highly secure, web based, reaserch specific, and customizable

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system that provides HIPPA complaint and study administration capabilities. The system is capable of storing basic protocol information (e.g. IRB approval dates, dates for annual renewals) and clinical trials research data, and it fully integrates study administration functionality including protocol tracking, patient registration, review committee tracking, and SAE tracking, with clinical data management functionality including electronic case report forms (eCRF) design, clinical data capture, protocol and regulatory compliance monitoring.

REDCap allows the investigator to define specific protocol requirements and generate data collection forms. REDCap permits specification of study protocols, management of patient enrollment, clinical data entry and viewing, and the generation of patient or study-specific reports based on time stamping. REDCap provides several reporting features specifically addressing the reporting requirements needed for the DSMC. Data may also be exported in a format suitable for import into another database, spreadsheets or analysis systems. REDCap is maintained and supported by Vanderbilt University Medical Center.

Risks

Complications of transbronchial cryobiopsy have been reported with variable incidence in several case series. According to recently reported experience at Vanderbilt Medical Center, main complications include pneumothorax (approximately 3%), bleeding (3-5%) and respiratory failure (2%). These are standard complications of the procedure and we do not expect that using radial ultrasonography additionally for localization will be associated with an increased rate of complications given the available data.

Benefits

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

Payment and Remuneration

Subjects will not be paid to participate in the study.

Costs

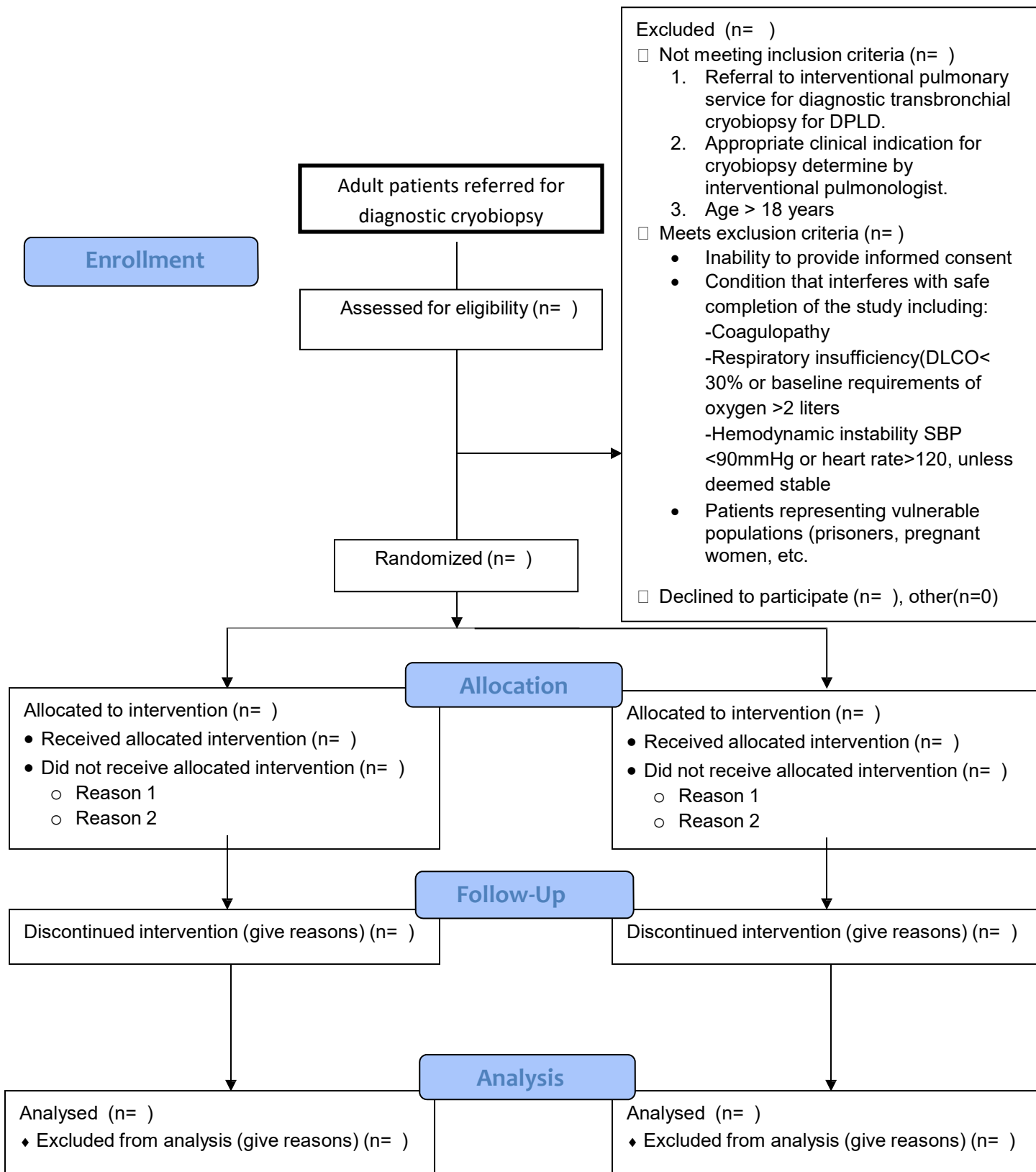
There will be no additional costs to subjects for participating in this study. Subjects and/or their insurance companies will be responsible for all care provided as part of the diagnostic transbronchial cryobiopsy as this service is part of the standard of care they would receive for their condition.

References

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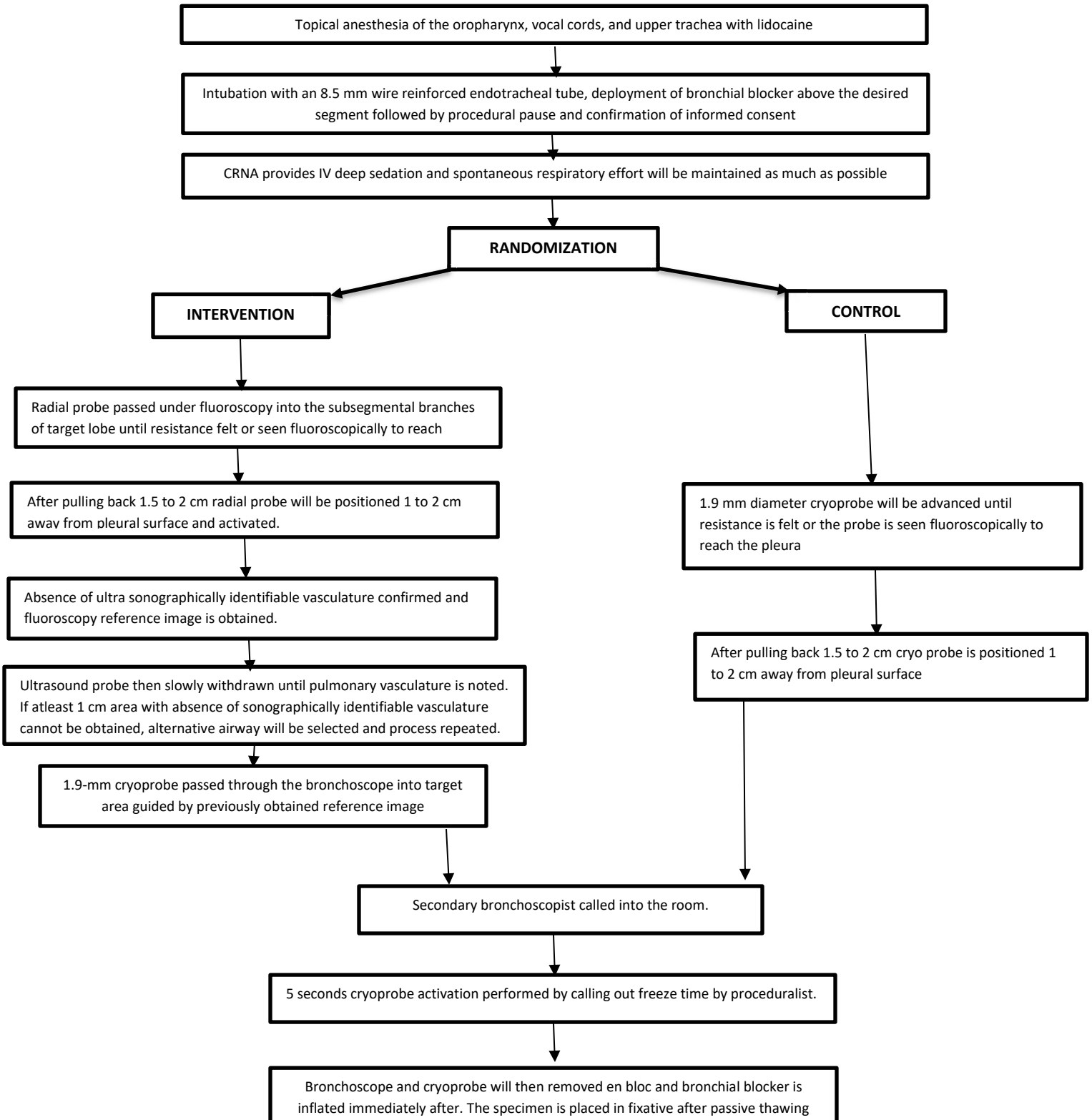
1. Lentz RJ, Taylor TM, Kropski JA, et al. Utility of Flexible Bronchoscopic Cryobiopsy for Diagnosis of Diffuse Parenchymal Lung Diseases. *Journal of bronchology & interventional pulmonology* 2017.
2. Hagemeyer L, Theegarten D, Treml M, Priegnitz C, Randerath W. Validation of transbronchial cryobiopsy in interstitial lung disease-interim analysis of a prospective trial and critical review of the literature. *Sarcoidosis vasculitis and diffuse lung disease* 2016;33:2-9.
3. DiBardino DM, Haas AR, Lanfranco AR, Litzky LA, Sterman D, Bessich JL. High complication rate after introduction of transbronchial cryobiopsy into clinical practice at an academic medical center. *Annals of the American Thoracic Society* 2017.
4. Poletti V, Casoni GL, Gurioli C, Ryu JH, Tomassetti S. Lung cryobiopsies: a paradigm shift in diagnostic bronchoscopy? *Respirology* 2014;19:645-54.
5. Lentz RJ, Argento AC, Colby TV, Rickman OB, Maldonado F. Transbronchial cryobiopsy for diffuse parenchymal lung disease: a state-of-the-art review of procedural techniques, current evidence, and future challenges. *Journal of thoracic disease* 2017;9:2186.
6. Memoli JSW, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. *CHEST Journal* 2012;142:385-93.
7. Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States. 2000 to 2011. *American journal of respiratory and critical care medicine* 2016;193:1161-7.
8. Pajares V, Puzo C, Castillo D, et al. Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: a randomized trial. *Respirology* 2014;19:900-6.
9. Ravaglia C, Bonifazi M, Wells AU, et al. Safety and diagnostic yield of transbronchial lung cryobiopsy in diffuse parenchymal lung diseases: a comparative study versus video-assisted thoracoscopic lung biopsy and a systematic review of the literature. *Respiration* 2016;91:215-27.
10. Kropski JA, Pritchett JM, Mason WR, et al. Bronchoscopic cryobiopsy for the diagnosis of diffuse parenchymal lung disease. *PloS one* 2013;8:e78674.
11. Babiak A, Hetzel J, Krishna G, et al. Transbronchial cryobiopsy: a new tool for lung biopsies. *Respiration* 2009;78:203-8.
12. Casoni GL, Tomassetti S, Cavazza A, et al. Transbronchial lung cryobiopsy in the diagnosis of fibrotic interstitial lung diseases. *PloS one* 2014;9:e86716.
13. Berim IG, Saeed AI, Awab A, Highley A, Colanta A, Chaudry F. Radial Probe Ultrasound-Guided Cryobiopsy. *Journal of bronchology & interventional pulmonology* 2017;24:170-3.

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PROCEDURE FLOWCHART



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