Official Title: **R**obotic versus **E**lectromagnetic Bronchoscopy for Pulmonary **L**es**I**on **A**ssessme**NT**: the RELIANT trial.

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Robotic versus **E**lectromagnetic Bronchoscopy for Pulmonary **L**es**I**on **A**ssessme**NT**: the RELIANT trial

Statistical Analysis Plan

Heidi Chen, PhD – Current Lead Biostatistician — **3/18/2024** Date

Heidi Chen, PhD – Current Lead Biostatistician — **09/28/2023** Date

Heidi Chen, PhD – Current Lead Biostatistician — August 15, 2023 Date

Heidi Chen, PhD – Current Lead Biostatistician — January 11, 2023 Date

Christopher J Lindsell, PhD – Initial Lead Biostatistician — July 12, 2022 Date

Change in Lead Biostatisticians occurred due to Dr. Lindsell's departure from VUMC on 12/31/2022.

Introduction

Advanced imaging and navigational guidance systems are often used to sample peripheral lung lesions. Electromagnetic navigation bronchoscopy (EMN) and shape-sensing catheter bronchoscopy (SSCB) are the most commonly used modalities. These devices are considered equivalent, usual care options for sampling peripheral pulmonary lesions, with similar side effect profiles. Despite EMN and SSCB being routinely used in clinical care there is no randomized data directly comparing these two platforms. This document describes the statistical analysis plan for a single center, open label, pragmatic, non-inferiority, cluster randomized controlled trial designed to evaluate the impact of these two platforms for improving clinical care for patients with peripheral lung lesions. This document has been prepared prior to final data collection and unblinding. It is hypothesized that the diagnostic yield of the Ion™ Endoluminal System (SSCB) is not inferior to the ILLUMISITE™ Platform (EMN) in patients undergoing bronchoscopy to biopsy a peripheral lung lesion (PPL).

Population and design considerations

Study Population:

Patients who are undergoing a navigational bronchoscopy for biopsy of a peripheral lung lesion and are ≥ 18 years of age at the time of the procedure will be included in this study. Patients will be excluded if they are enrolled in a different study requiring use of one of these specific platforms or if they decline to participate.

Study Design:

This is a single center, open label, pragmatic, non-inferiority, cluster randomized controlled trial comparing clinical outcomes between patients assigned to receive a diagnostic bronchoscopy with either the Ion™ Endoluminal System (SSCB) or the ILLUMISITE™ Platform (EMN) platform.

Randomization:

Operating rooms are set up each morning with one of the two devices for the day's of pre-scheduled procedures. Cluster randomization will be used for this study given impracticability of patient-level 1:1 parallel randomization in these circumstances. The ILLUMISITE™ Platform (EMN) and Ion™ Endoluminal System (SSCB) will be randomly allocated to our two operating rooms each day. All patients undergoing a navigational bronchoscopy will have their procedure performed with the platform assigned to their operating room for the day. A biostatistician not involved in patient care will generate the randomization sequence. Random permuted blocks may be used to ensure balanced cluster allocation. A bronchoscopy scheduler with no knowledge of the allocation scheme will schedule each patient into one of the two operating rooms. Allocations will be concealed in sealed envelopes which will be opened every morning by the operating room staff preparing the rooms.

Sample Size Considerations:

The study team performs 1-4 guided bronchoscopies per day (average of 2 per day) and approximately 400 per year. Based on data from prior studies and the study team's published data, we estimated the diagnostic yield of EMN to be 80%. The diagnostic yield of SSCB has not been fully elucidated, but published data suggest an overall diagnostic yield of 80% as well. Assuming the diagnostic yield for the ILLUMISITE™ Platform (EMN) is 80%, with a non-

inferiority margin set at 10%, cluster size of 2, and no intracluster correlation, we need 202 clusters (operating days) to have an 80% power to conclude noninferiority at a one-sided type I error rate of 5%, which corresponds to a target of 425 subjects to reach 202 per arm. The noninferiority margin has been chosen based on what would be considered a clinically significant difference (or, put differently, a difference which might influence a hospital to purchase one platform over the other). In case our average cluster size does not reach 2, we will plan to increase the number of clusters to meet our target enrollment of 425 subjects to reach 202 per arm.

Interventions
All patients meeting the eligibility criteria for this study will be enrolled. Cluster randomization will be used, and patients will be assigned to one of the two comparator arms:

a) Ion™ Endoluminal System (SSCB)

b) ILLUMISITE™ Platform (EMN)

Outcomes
Primary Outcome
The primary endpoint will be diagnostic yield, defined as the proportion of procedures that results in acquisition of lesional tissue.

Lesional tissue is defined by the presence of pathological findings that readily explain the presence of a pulmonary lesion. The following common pathological findings are pre-specified:

- Malignancy
- Specific benign pathologic finding including
    - Organizing pneumonia
    - Frank purulence/robust neutrophilic inflammation
    - Granulomatous inflammation
    - Other specific benign findings such as hamartoma, amyloidoma or other uncommon causes of PPLs with distinctive pathological patterns.

Biopsies not meeting any of the above lesional pathological criteria will be adjudicated as not meeting the primary outcome (not being “diagnostic"), including biopsies with normal lung parenchyma or airway components on biopsy, atypia not diagnostic of malignancy, or non-specific inflammation. A blinded panel will review all non-malignant biopsies at the end of accrual to confirm specific benign or non-diagnostic findings on biopsy. Procedures will be adjudicated as not meeting the primary outcome if the procedure starts but biopsies are not obtained (due to failure to navigate to the lesion, or complication, or equipment failure). A procedure will be considered started at induction of general anesthesia.

Biopsies obtained without the use of EMN or SSCB (e.g., sampling of central lymph nodes using the linear endobronchial ultrasound bronchoscope) will not be included in the diagnostic yield calculations. In case of repeat bronchoscopies, only the index bronchoscopy will be included in the diagnostic yield calculation.

Secondary Outcomes
There is one secondary outcome for the trial, which will be collected during the bronchoscopy procedure.

a) Duration of procedure (in minutes), defined as time from the start of airway registration to the removal of the bronchoscope after completion of navigation procedures.

Exploratory Endpoint(s)
There are three exploratory endpoints that are prespecified. These can be collected during and immediately after the bronchoscopy procedure, and/or during the follow-up period.

a) Need for additional diagnostic procedures. Any diagnostic procedure performed within 12 months of the study bronchoscopy that targets the same peripheral lesion (including repeat bronchoscopy, transthoracic needle biopsy, or surgical lung biopsy) will be considered an additional diagnostic procedure.

1. Repeat biopsies of lesions determined to be malignant by study bronchoscopy which are 1) performed specifically to obtain additional tissue for further testing but that does not change the malignant diagnosis, or 2) therapeutic surgical resection of such lesions, will not be considered additional diagnostic procedures.

b) Radiation exposure, defined as radiation dose delivered to the patient during the study bronchoscopy, recorded as a dose area product (mGy/cm2).

Diagnostic accuracy
Diagnostic accuracy will be assessed for the two devices. Lesions will be categorized as positive (malignant) lesions or negative (specific benign diagnosis). The criterion standard for a negative diagnosis will be no evidence of malignancy at 12-month follow-up (no interval biopsy diagnostic of malignancy, regression on CT or stable size with no plan for repeat diagnostic procedure).

Safety outcome
The main safety outcome for this trial is occurrence of procedure complication(s), defined as the occurrence of any of the following: respiratory failure, pneumothorax, anesthetic complications, and bronchopulmonary hemorrhage.

Safety outcomes will be reported overall and by type.

Analysis dataset
The analysis for the trial will use a intent-to-treat approach. Participants will be evaluated by treatment group as assigned regardless of what was delivered; participants will be excluded if their procedure did not begin, defined as the start of the navigation procedure itself. All eligible participants will be included.

The safety analysis dataset will group participants by device used, regardless of assignment.

Statistical Approach
Our initial analysis will be descriptive in nature, summarizing information that characterizes the cohort and the outcomes. Then, we will proceed with inferential analysis. No interim analyses are planned.

Descriptive Analysis
To characterize the study sample, baseline demographic and clinical data will be described overall and by group. Categorical variables will be described using frequencies and proportions, and continuous variables will be described using means and standard deviations or medians and interquartile ranges, as appropriate. Missingness will be reported for each variable. At a minimum, the following variables will be described at time of enrollment:

- Age (years)
- Gender (male, female, unknown)
- Race (African American, Asian/Pacific Islander, Caucasian, Multiple, Native American, Other, Unknown)
- Ethnicity (Hispanic, Non-Hispanic, Unknown)
- History of cancer (yes/no)
- Smoking History (current, former, never)
- Body mass index (BMI)
- Lesion characteristics
    - Size (mm)
    - Location (middle vs peripheral)
    - Upper lobe (yes/no)
    - Density (solid, part solid, ground glass opacity)
    - Distance from pleura (cm)
    - Bronchus sign present (yes/no)
- Procedure details

- Rapid onsite evaluation (yes/no)
- Operator
- Digital tomosynthesis (yes/no)
- Cone beam computed tomography (yes/no)
- Biopsy tools

We will describe the outcome variables overall and grouped by study arm using the same approach as for the demographic data. Summary statistics and graphical representations may be displayed, and missingness will be reported for each variable. No statistical comparisons between groups will be done for this descriptive analysis.

Primary analysis

The primary analysis for the trial will use an intent-to-treat approach. Participants will be evaluated by treatment group as assigned regardless of what was delivered. All eligible participants will be included.

The primary outcome variable (diagnostic yield) will be compared between groups using a generalized linear mixed model with one-sided test. The primary model will be covariate adjusted, including fixed effects for device assignment, lesion size, density, peripheral location, and bronchus sign, and a random effect for operator. Should the model demonstrate signs of overfitting, covariates may be selected based on priority order (device assignment, lesion size, density, peripheral location, bronchus sign, operator).

If non-inferiority is demonstrated, we will proceed with a superiority analysis using the same approach as the non-inferiority analysis, an adjusted generalized linear mixed effects model with the same covariates used in the primary analysis. No adjustment will be made for multiplicity. The superiority analysis would be conducted at a one sided p-value of 0.05.

Secondary and exploratory analysis

A sensitivity analysis using a *per protocol* approach will be conducted to analyze participants based on the device used. We will use the same approach as the primary analysis, an adjusted generalized linear mixed effects model using the same covariates.

The secondary outcome, procedure duration, will be compared between study groups using a linear mixed model. If the procedure duration is skewed, alternative models may be pursued,

such as a cox regression. The primary model will be covariate adjusted following a similar approach to the analysis of the primary outcome. Analysis of the exploratory endpoints will follow a similar approach.

Safety analysis

Procedure complications are expected in usual care, although uncommon. We will report all procedure complications for each device, overall and by type. If event rates exceed 5%, we may proceed with a comparative analysis, which will involve a generalized linear mixed regression model for binary outcomes as specified for the main analysis, with the exception that covariate adjustment may not be possible. The safety analysis dataset will group participants by device used, regardless of assignment.

All model results will be summarized with point estimates and 95% confidence intervals (CIs), which will be emphasized over p-values when reporting the results for secondary outcomes. No adjustments for multiplicity will be made.

Differential effects

To determine whether differences in outcomes are dependent on baseline characteristics, we will introduce interaction terms into the models developed for the main analysis. Specifically, we will test the interaction between device assignment and the subgrouping variable. Each variable will be tested one by one, such that all main effects but only one interaction term is included at a time. The following putative subgrouping variables are prespecified:

- Nodule size (continuous, treatment effects will be estimated at 1.5cm and 3cm)
- Presence of bronchus sign
- Solid vs subsolid nodule
- Peripheral vs central location – *Peripheral defined as outer 1/3 of chest*

Missingness on the primary or secondary outcome is not expected due to the proximity of its measurement with the procedure and its integration into clinical documentation. Procedures missing the primary outcomes will be considered not diagnostic. Missing covariates will be imputed using multiple imputation with predictive mean matching. There may be missingness on exploratory outcomes. For missing exploratory outcomes, a complete case analysis will be performed.

Diagnostic accuracy

Diagnostic test statistics (e.g., sensitivity, specificity, predictive values, likelihood ratios) will be reported for the two devices. In addition, accuracy of the diagnosis may be modeled using a generalized linear model to explore whether participant or lesion features are predictive of procedure success, as described for the differential effects analysis.

Summary

The results of this study will help to determine whether there is a difference between these two diagnostic bronchoscopy platforms for patient outcomes. The analysis approach we describe is selected based on the trial's pragmatic nature and specifically the intent to understand if the diagnostic yield of the Ion™ Endoluminal System (SSCB) is not inferior to the ILLUMISITE™ Platform (EMN) in patients undergoing bronchoscopy to biopsy a peripheral lung lesion.

Version and Revision Log

7/12/2022	Version 1: developed with and approved by Christopher J. Lindsell, PhD.
1/11/2023	Version 1: Dr. Lindsell departed VUMC and Heidi Chen, PhD became the current lead biostatistician and reviewed and approved the SAP.
8/14/2023	Version 2: Edits developed with and approved by Heidi Chen, PhD Revisions: • Adding the exclusion criterion that subjects can decline to participate. • Minor clarifications to the primary, secondary, and safety outcomes. • Adjustments to the analysis, differential effects, and missingness sections to be in alignment with the protocol manuscript.
9/28/2023	Version 3: Edits developed with and approved by Heidi Chen, PhD Revisions: • Clarifying the anticipated number of patients and clusters to be enrolled for this study.
3/18/2024	Version 4: Edits developed with and approved by Heidi Chen, PhD Revisions: • Clarifying the anticipated number of patients to ensure 202 patients will be enrolled per arm.