PennState

HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:
Piloting a virtual navigation (VN) system for bronchoscopic lung nodule sampling

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Version Date:

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December 7, 2022

Clinicaltrials.gov Registration #:

Provide the registration number for this study, if applicable. See "HRP-103- Investigator Manual," under "ClinicalTrials.gov" for more information.

NCT05599321.

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3. **PROTOCOL REVISIONS:**

[1] This template satisfies AAHRPP elements 1.7.B, I.8.B, I-9, II.2. A, II.2.I, II.3.A, II.3.B, II.3.C-II.3.C.1, II.3.D-F, II.4.A, III.1.C-F, II.2.D

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If you need help…

All locations:
Human Research Protection Program
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The 330 Building, Suite 205
University Park, PA 16802-7014
Phone: 814-865-1775
Fax: 814-863-8699
Email: irb-orp@psu.edu
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1.0 Objectives

1.1 Study Objectives

Describe the purpose, specific aims or objectives. State the hypotheses to be tested.

This preface is to provide a historical perspective, which includes the connection between the current submission and the previous protocol submitted under IRB number PRAMS020349-A . IRB Protocol PRAM20349 -A was originally submitted on 1/31/2005, approved March 8, 2005, and referenced a research protocol dated 2/10/2005. The unchanged long range study goal is to improve bronchoscopy performance and diagnostic yield using computer-based enhancements of existing (clinical) images. This work has been performed under three consecutive NIH grants, including the current NIH R01 grant. The current R01 NIH funded grant is entitled "Multimodal Image Guided Intervention System for Lung Cancer Diagnosis and Staging."

The overall purpose is to evaluate the role of a Virtual Navigation (VN) system (the Virtual Navigator) in the bronchoscopic evaluation and tissue sampling of lung cancer and other chest lesions at Hershey Medical Center (HMC). The long-term goal of this research program is to improve bronchoscopy performance and diagnostic yield using computer-based enhancements of existing clinical images. While the overall objective and long-term goal of this research program are unchanged, the aims and research methods have been modified to adapt to the technical advances in clinical images (PET/CT scans) and bronchoscopy (endobronchial ultrasound/EBUS). These advances create the need for multimodal image guided intervention systems.

The main technical objective of the NIH grant is to develop and test the Virtual Navigator system, a non-invasive diagnostic device. Prior to this current protocol, we have already completed a number of laboratory studies, controlled animal studies, and studies drawn on retrospectively collected human data (collected under the IRB Protocol entitled "Repository of Lung Cancer Diagnostic Procedure Images," Rebecca Bascom (PI), study ID = PRAMS21405EP.

For this current IRB protocol, our objective is to conduct prospective human studies to compare the optimized Virtual Navigator system to state-of-the-art practice. We will compare our system to state-of-the-art bronchoscopy/EBUS practice through three aims:

Aim 1: conduct the first complete end-to-end real-time runs of the system through our University Hospital's lung-cancer clinical work flow. The goals are to validate system safety and functionality in a live clinical setting and to optimize the system for the human studies of Aims 2 and 3.

Aim 2: for peripheral-tumor diagnosis, we determine if diagnostic biopsy yield increases with the optimized VN system compared to historical controls. The study is driven by the following sub-hypothesis: Image-guided bronchoscopy (live cases) increases diagnostic biopsy yield over state-of-the-art bronchoscopy practice (historical controls). The image-guided bronchoscopy will not constitute a diagnostic procedure without confirmation by another medically-established diagnostic procedure.

Aim 3: for central-chest nodal staging, we ascertain if nodal staging becomes more comprehensive. The following sub-hypothesis motivates the study: Image-guided bronchoscopy (live cases) enables more thorough nodal staging than state-of-the-art bronchoscopy practice (historical controls).

1.2 Primary Study Endpoints

State the primary endpoints to be measured in the study.

Clinical trials typically have a primary objective or endpoint. Additional objectives and endpoints are secondary. The endpoints (or outcomes), determined for each study subject, are the quantitative measurements required by the objectives. Measuring the selected endpoints is the goal of a trial (examples: response rate and survival).

For Aim 1, the primary study endpoint is to validate the optimized VN system's safety and functionality during a live bronchoscopy procedure. To do this, we will observe the VN system's functionality during the study (Does it crash? Is it too slow? Are there errors?), we will note how the mobile computer fits into the surgical suite's set-up (Do we need to move the computer to a different location?), and we note physician feedback on the system (Are the presented images clear? Too small? Superfluous? Does the physician find them useful?). In addition, we record all data from each study and use these data to note other observations. Based on this information, system- and work-flow modifications will be made to improve the system.

(Note that this is a standard series of tests to perform before going into "production mode" for the prospective studies. Note that prior to these studies, the system prototype has already undergone a large number of tests to ascertain its functionality, via laboratory studies, studies drawing on retrospective human data (as encountered during a live procedure), and with controlled animal studies. Thus, we already will have a functioning prototype, with considerable verified reliability.)

For Aim 2, the primary study endpoint is to measure the diagnostic biopsy yield for peripheral tumor sampling (live studies) as compared to historical controls.

For Aim 3, the primary study endpoint is to measure the number of lymph nodes visited during nodal staging (live studies) as compared to historical controls.

Secondary Study Endpoints

State the secondary endpoints to be measured in the study.

Aim 1 does not have secondary endpoints.

For Aim 2, secondary study endpoints are number of biopsy samples per tumor; pathologic interpretation of the clinical samples (malignant, non-malignant, indeterminate); complications (e.g., pneumothorax); distance of a biopsy location from computed optimal biopsy site; and procedure time (total and per tumor). We will compare live cases and historical controls.

For Aim 3, secondary study endpoints are number of nodal sites reached; diagnostic biopsy yield (diagnosis made by TBNA); number of biopsies per lymph node; adequacy of biopsy samples; complications; distance of a biopsy site from the computed optimal biopsy site; and procedure time (total and per node). We will compare live cases and historical controls.

2.0 Background

2.1 Scientific Background and Gaps

Describe the scientific background and gaps in current knowledge.

For clinical research studies being conducted at Penn State Health/Penn State College of Medicine, and for other non-PSH locations as applicable, describe the treatment/procedure that is considered standard of care (i.e., indicate how patients would be treated in non-investigational setting); and if applicable, indicate if the treatment, drug, or device is available to patient without taking part in the study.

Lung cancer is the leading cause of U.S. cancer death in men and women, and approximately 500,000 bronchoscopies are done each year in the United States for diagnosis and staging of lung cancer. Documenting biopsy-proven cancer is important to determine lung cancer stage and management options.

Given its safety profile and versatility, bronchoscopy has emerged as the preferred approach for lung-cancer diagnosis and staging. Bronchoscopy enables minimally invasive access to both peripheral tumors and central-chest lymph nodes, with few complications. To procure a tissue biopsy of a region of interest (ROI) via bronchoscopy, the physician follows three steps: 1. Plan an airway navigation route to the site, using the patient's CT scan. 2. Navigate the bronchoscope through the airway tree to an airway near the site using the preplanned route. 3. Biopsy the site by selecting an airway-wall point for needle puncture.

It is well known that physicians poorly translate CT-based airway routes to live bronchoscopy and their skill in navigating a bronchoscope along several airways varies greatly. To aid with planning and navigation, image-guided navigation systems have become popular in the past five years, including a major contribution by our group. These systems draw on the concept of virtual bronchoscopy (VB), whereby the patient's CT scan serves as a 3D "virtual" chest space. To use such a system, a procedure plan, consisting of airway routes leading to each ROI, is first derived from the patient's CT scan. Next, during the live procedure, the system's "virtual bronchoscope" navigates through virtual space, presenting CT-based VB views resembling "real" videobronchoscope views along an ROI's preplanned airway route. Meanwhile, the physician synchronizes (registers) the "real" bronchoscope's position to the VB views.

Two related types of systems— electromagnetic navigation, which requires extra EM hardware and disposables, and image-based VB navigation (VBN)—are available, giving similar performance. Image-guided navigation systems have proven to equalize physician skill differences while also enabling a task they heretofore could not perform—a clear example of the potential of image-guided intervention systems. Since most tumors and all lymph nodes are extraluminal (outside the airways), needle biopsy, referred to as transbronchial needle aspiration (TNBA), has largely been performed blindly. To aid with biopsy, two complementary forms of endobronchial ultrasound (EBUS) enable local extraluminal viewing of ROIs. For a peripheral tumor, the physician navigates a small-diameter (< 4 mm) videobronchoscope into an airway near the tumor and then inserts a radial EBUS probe (RP-EBUS) into the bronchoscope's working channel to give 360^{o} field-of-view (FOV) extraluminal images for visualizing the tumor. For central-chest lymph nodes, a larger (6.9 mm) integrated bronchoscope incorporating video and a convex-probe EBUS (CP-EBUS) into one device is used. The physician uses video to navigate the device near a lymph node and then CP-EBUS to see 50^{o} FOV images for confirming the node's location.

Gaps:

The first limitation of image-guided bronchoscopy systems is that they offer no guidance for selecting biopsy sites, especially as it pertains to using peripheral EBUS. In particular, they give no guidance in coordinating the use of video bronchoscopy and EBUS or in positioning the EBUS for effective biopsy-site selection. The second limitation of image-guided bronchoscopy systems is that they offer no guidance for efficient coordinated navigation to many nodal stations. This limitation especially affects prospective stage-1 patients, where establishing a correct early-stage decision is critical.

We believe our proposed Virtual Navigator system will greatly reduce the number of inconclusive bronchoscopies in the long run, thereby giving more accurate and timely diagnosis/staging decisions. In particular, our system overcomes the two critical barriers limiting existing image-guided bronchoscopy systems by offering new methods for: 1) coordinated guidance of video bronchoscopy and EBUS for

accurate biopsy targeting; and 2) efficient navigational guidance for complete sampling of the central-chest nodal stations.

2.2 Previous Data

Describe any relevant preliminary data.

Below, we summarize our previous project's major innovations. The studies for this work were completed under our previous NIH R01 grant under IRB protocol PRAMS020349-A.

We have devised a wide range of software methods, incorporated into the Virtual Navigator system. We have devised an optimal route-planning method for bronchoscopic navigation. The optimization incorporates constraints imposed by the airway tree, videobronchoscope, TBNA needle, and obstacles to avoid (vessels, lungs). Over a 30-patient study, our method enabled a mean bronchoscope navigation depth = 7.3±2.3 airways versus 5.7±1.3 airways achieved by the competing Olympus BfNAVI VBN system. Also, a 3D CT-based chest model provides anatomical cues for procedure planning and guided bronchoscopy. Our methods for deriving this model include the airway tree, airway centerlines and endoluminal surfaces, lungs, vasculature, bones, and thoracic cavity. The thoracic cavity is especially important, as it focuses attention on the region accessible to bronchoscopy.

Finally, we developed and extensively used several automatic and semi-automatic CT-based software methods for rapid ROI definition, including the 3D live wire, single-click region growing and active-contour analysis, and Otsu-based thresholding, along with supplemental region painting/erasing methods.

A CT-video software registration method drives the system, enabling 300 frames/sec registration of VB views to video for real-time navigational guidance, while a global CT-to-video registration method corrects in-flight navigation errors. An autonomous image guidance strategy allows the physician to navigate the bronchoscope without technician assistance. The strategy augments preplanned airway routes with step-by-step rotate/flex/advance bronchoscope-navigation maneuvers. During bronchoscopy, the system displays the maneuvers. An ergonomic study found that 96% of the presented real-time computed guidance views offered acceptable guidance, while a patient study achieved much faster navigation than the more labor-intensive technician-assisted guidance systems.

A patient's 3D high-resolution chest CT forms the backbone of the virtual chest space for procedure planning and guided bronchoscopy. PET imaging, however, can help prioritize CT ROIs as suspiciously metastatic PET-avid "hot spots," where PET is derived from a co-registered free-breathing whole-body CT/PET study. We fuse chest CT and PET through a multimodal deformable registration of the whole-body CT/PET and breath-hold chest CT. The 3D spatially varying deformation model, derived within the space of the thoracic cavity, then maps the PET into 3D chest CT space. The resulting fused CT/PET volume enables CT/PET fusion visualization for plan preview and guided bronchoscopy, via multimodal 3D surface/2D-section rendering, etc.

We prototyped the first rudimentary multimodal system for navigation and CP-EBUS guidance for the central chest. In a pilot patient study, we guided CPEBUS localization of 60/63 (95%) ROIs, where a preliminary 2D method registers the virtual CT/PET chest space to 2D CP-EBUS frames. A new CP-EBUS algorithm automatically segments 2D CP-EBUS sequences and enables 3D reconstruction. A novel multimodal virtual bronchoscope extends the standard CT/video virtual bronchoscope to multimodal imaging by providing CT-based virtual video and EBUS views that mimic the real CP-EBUS bronchoscope's two data sources.

A CT-based Nodal-Station Definition System automatically delineates the 3D IASLC nodal stations and helps isolate lymph nodes from a patient's 3D chest CT scan. In a ground-truth study, 93% of the computed stations were correctly located and 96% of lymph nodes received correct station labels.

Perhaps the biggest testament to our first project's success is having our CT-based procedure planning and virtual-bronchoscopic navigation technology translated into clinical practice. Through a Penn State licensing agreement, Broncus (sic) Medical, San Jose, CA, markets four FDA approved devices (planning and VBN guidance systems for the Lungpoint and Archimedes platforms) that have been applied to thousands of patients worldwide. They are a major reason for the recent international acceptance of image-guided bronchoscopic navigation systems, as evidenced by the following publication list referring to these systems. Broncus's LungPoint was used in the multi-center AQuIRE study for peripheral tumor biopsy. Also, our CT/PET fusion technology is also now entering technology transfer to Broncus. Finally, we have made three ground-truth databases publicly available for: a) CT/PET chest lesion analysis; b) CP-EBUS image segmentation; and c) chest CT-based lymph-node analysis. See "Links/Public Databases" under http://www.mipl.ee.psu.edu/.

2.3 Study Rationale

Provide the scientific rationale for the research.

The number of pre-screened lung-cancer patients will increase greatly in the near term. These patients—not to mention the more "traditional" patient population—demand timely, effective follow-on disease diagnosis and staging. Only in this way can they then be prescribed the treatment they deserve to improve their chance of survival from this aggressive disease. It is well-known that malignant lung tumors double in size rapidly. In fact, it can be strongly argued that CT-based early cancer screening will not realize its promise without new diagnosis/staging tools. Notably, our system could equalize physician skill in using EBUS and enable a new task (complete nodal staging), making these tools accessible to a wider physician group.

Thus, the long-term transformative innovation we hope to contribute is a system enabling much more effective lung-cancer disease diagnosis and staging than current state-of-the-art tools. Our proposal works toward this goal by constructing a system with the following specific innovations:

1. Optimal multimodal procedure planning constructs a plan tailored specifically to a patient for efficient, accurate diagnosis and staging in a single minimally invasive bronchoscopy procedure. For a peripheral tumor, the airway route becomes augmented with the all-important final destination designating the optimal biopsy target, as dictated by the bronchus sign and other constraints imposed by the devices and chest anatomy. For the central chest, the method derives an airway route customized for efficient navigation through the IASLC nodal stations, based on the patient's specific tumor/node situation and clinical staging guidelines; it also provides biopsy targets for each nodal-station stop along the route—in this way, a potentially confusing task becomes more straightforward. Finally, for both peripheral and central bronchoscopy, the method derives device maneuvers to go with the airway routes for coordinated manipulation of the videobronchoscope and EBUS.

2. For biopsy of peripheral tumors and central-chest lymph nodes, a fusion-based video/EBUS guidance method directs device usage and combines the available videobronchoscopy and EBUS data streams (as opposed to discarding them as done currently) into a model about the optimal biopsy-target region. The resulting fused 3D endoluminal/mosaic model then provides a means for robust biopsy-site selection.

3. An efficient graphics-based guidance protocol directs a sequential station-by-station process for complete central-chest nodal staging. Endoluminal bronchoscopy-centric station targets are presented to facilitate more intuitive CP-EBUS sweeps of nodal stations. Also, a live bronchoscopy path history is maintained to alleviate confusion as to which stations have been visited. In this way, the most clinically significant stations are biopsied first and the procedure can terminate once sufficient results are obtained. Given our long experience in large-scale image-guided system design, software development, clinical validation, and translation to practice, we are optimistic that we can achieve the project's goal.

3.0 Inclusion and Exclusion Criteria

Create a numbered list below in sections 3.1 and 3.2 of criteria subjects must meet to be eligible for study enrollment (e.g., age, gender, diagnosis, etc.).

Vulnerable Populations:

Indicate specifically whether you will include any of the following vulnerable populations in this research. You MAY NOT include members of these populations as subjects in your research unless you indicate this in your inclusion criteria because specific regulations apply to studies that involve vulnerable populations.

The checklists referenced below outline the determinations to be made by the IRB when reviewing research involving these populations. Review the checklists as these will help to inform your responses throughout the remainder of the protocol.

- **Children –**Review "HRP-416- Checklist - Children"
- **Pregnant Women** – Review "HRP-412- Checklist - Pregnant Women"
- **Cognitively Impaired Adults-** Review "HRP-417- Checklist - Cognitively Impaired Adults"
- **Prisoners-** Review "HRP-415- Checklist - Prisoners"
- **Neonates of uncertain viability or non-viable neonates-** Review "HRP-413- Checklist - Non-Viable Neonates" or "HRP-414- Checklist - Neonates of Uncertain Viability"

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3.1 Inclusion Criteria

Create a numbered list of the inclusion criteria that define who will be included in your final study sample (e.g., age, gender, condition, etc.)

For the live cases:
The subject population includes patients whose clinical evaluation requires a diagnostic bronchoscopy for evaluation of parenchymal or mediastinal abnormalities. This patient population is typically 40-70 years old, but includes patients from age 18 and over, with no upper age limit.
Inclusion criteria are:
1) a planned clinical bronchoscopy to evaluate abnormal lung parenchyma and/or central chest lymph nodes;
2) a clinical CT scan performed at Hershey Medical Center that meets technical specifications and is available on the Radiology research server.
3) (Optional, use if available) CT/PET images that meet technical specifications and are available on the Hershey Medical Center clinical image storage system. Note that only clinically prescribed scans are used in the study; no new scans are required for the study.

For the historical controls, inclusion criteria are:

1) Prior clinical bronchoscopy to evaluate abnormal lung parenchyma and/or central chest lymph nodes for evaluation of possible lung cancer
2) Prior clinical CT scan with radiologic interpretation present in the medical record

3.2 Exclusion Criteria

Create a numbered list of the exclusion criteria that define who will be excluded in your study.

For the live cases:
1) Special classes of subjects that will be excluded are pregnant women because clinical CT scans and CT/PET studies are avoided because of the potential for radiation injury to the fetus. 2) Mentally incompetent subjects will be excluded. They will be identified as such because their treating clinician will have deemed them unable to provide consent for their clinical procedure. The clinical record will indicate whether the patient is providing consent or a surrogate decision-maker has been needed. Patients with a surrogate decision-maker will be excluded.
3) We will exclude prisoners and institutionalized individuals because their autonomy is compromised by their status, and the study provides no direct benefit from which they would be excluded. Individuals who become prisoners or are institutionalized after giving consent but before their diagnostic procedure would also be excluded. Their clinical record will identify if they are in custody.
4) Children are not part of this project because they do not get lung cancer. Therefore, we do not provide processes for meeting requirements for parental permission and child assent.

For the historical controls, exclusion criteria are:
1) Insufficient clinical data for comparison and analysis

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Insert subject withdrawal criteria (e.g., safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, disease progression, etc.).

Not applicable.

3.3.2 Follow-up for withdrawn subjects

Describe when and how to withdraw subjects from the study; the type and timing of the data to be collected for withdrawal of subjects; whether and how subjects are to be replaced; the follow-up for subjects withdrawn from investigational treatment.

Not applicable.

4.0 Recruitment Methods

- Upload recruitment materials for your study in CATS IRB (http://irb.psu.edu). **DO NOT** include the actual recruitment wording in this protocol.
- StudyFinder: If StudyFinder (http://studyfinder.psu.edu) is to be used for recruitment purposes, separate recruitment documents do not need to be uploaded in CATS IRB. The necessary information will be captured from the StudyFinder page in your CATS IRB study.
- Any eligibility screening questions (verbal/phone scripts, email, etc.) used when contacting potential participants must be uploaded to your study in CATS IRB (http://irb.psu.edu).

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4.1 Identification of subjects

Describe the source of subjects and the methods that will be used to identify potential subjects (e.g., organizational listservs, established recruitment databases, subject pools, medical or school records, interactions during a clinic visit, etc.). If not recruiting subjects directly (e.g., database query for eligible records or samples) state what will be queried, how and by whom.

StudyFinder:

- If you intend to use StudyFinder (http://studyfinder.psu.edu) for recruitment purposes, include this method in this section.
- Information provided in this protocol, including the description of study procedures, compensation, and recruitment, needs to be consistent with information provided on the StudyFinder page in your CATS IRB study.

For Penn State Health submissions using Enterprise Information Management (EIM) for recruitment, and for non-Hershey locations as applicable, attach your EIM Design Specification form in CATS IRB (http://irb.psu.edu). See "HRP-103- Investigator Manual, Study Recruitment" for additional information. **DO NOT** include the actual recruitment material or wording in this protocol.

Subjects will be patients of clinicians in the Divisions of Pulmonary, Allergy and Critical Care Medicine and Thoracic Surgery of the Milton S. Hershey Medical Center. Patients will be identified by screening medical records of upcoming Pulmonary and Thoracic Surgery physician visits and bronchoscopic procedures. The records of clinic patients are pre-screened to determine their eligibility. The clinical bronchoscopist is informed of the eligibility of their patient for the research study and assents to recruitment. Note that all physicians involved in identifying potential subjects are members of the research team.

4.2 Recruitment process

Describe how potential subjects first learn about this research opportunity or indicate as not applicable if subjects will not be prospectively recruited to participant in the research. Subject recruitment can involve various methods (e.g., approaching potential subjects in person, contacting potential subjects via email, letters, telephone, ResearchMatch, or advertising to a general public via flyers, websites, StudyFinder, newspaper, television, and radio etc.). **DO NOT** include the actual recruitment material or wording in this protocol.

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4.2.1 How potential subjects will be recruited.

For potential participants in the live case portion of the study, Phase 1 of the consent happens by telephone or in person. Patients will hear a verbal description of the research study, its purposes and procedures, presented by one the Co-Investigators listed on the consent form. In Phase 2 they read and sign a written consent form and are given a signed copy of the consent form. In some cases, the study may be explained to the patient over the telephone, and verbal consent obtained to begin image retrieval and processing. In this case, arrangements for a face to face meeting, completion of signed consent, and providing the patient with a copy of the signed form will occur in advance of using the images as part of a bronchoscopy. This is typically done to align the pace of the research with the urgency of obtaining a clinical diagnosis, especially if cancer is suspected.

4.2.2 Where potential subjects will be recruited.

For potential participants in the live case portion of the study, subjects will be recruited either by telephone or during visits with their Pulmonary and/or Thoracic Surgery physicians.

4.2.3 When potential subjects will be recruited.

For potential participants in the live case portion of the study, subjects will be recruited prior to their scheduled bronchoscopy.

4.2.4 Describe the eligibility screening process and indicate whether the screening process will occur before or after obtaining informed consent. Screening begins when the investigator obtains information about or from a prospective participant in order to determine their eligibility. In some studies, these procedures may not take place unless HIPAA Authorization is obtained OR a waiver of HIPAA Authorization when applicable for the screening procedures is approved by the IRB. [*For FDA regulated studies, consent for any screening activities would need to be obtained prior to screening unless specifically waived by the IRB.]*

For potential participants in the live case portion of the study, patients will be identified by screening medical records (including age, diagnosis, date of CT scan, date of PET scan, gender, race/ethnicity) of upcoming bronchoscopic procedures. The records of clinic patients are pre-screened to determine their eligibility. The research technical team members at the MIPL (Multidimensional Image Processing Lab, 204 Electrical Engineering West, William Higgins, PI) at University Park will log on to a research server to determine whether there is a research quality copy of the clinical chest CT scan for the potential participant. If so, the treating physician is informed of the eligibility of their patient for the research study and is asked for permission to assent to recruitment.

For potential historical controls, patients will be identified by screening medical records (including age, diagnosis, date of CT scan, date of PET scan, gender, race/ethnicity) of past bronchoscopic procedures between 2017-2022.

5.0 Consent Process and Documentation

Refer to the following materials:

- The “HRP-090- SOP - Informed Consent Process for Research” outlines the process for obtaining informed consent.
- The “HRP-091– SOP - Written Documentation of Consent” describes how the consent process will be documented.
- The “HRP-314- Worksheet - Criteria for Approval” section 7 lists the required elements of consent.
- The “HRP-312- Worksheet - Exemption Determination” includes information on requirements for the consent process for exempt research. In addition, the CATS IRB Library contains consent guidance and templates for exempt research.
- The CATS IRB library contains various consent templates for expedited or full review research that are designed to include the required information.
- Add the consent document(s) to your study in CATS IRB (http://irb.psu.edu). Links to Penn State’s consent templates are available in the same location where they are uploaded. **DO NOT** include the actual consent wording in this protocol.

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5.1 Consent Process:

Check all applicable boxes below:

☒ **Informed consent will be sought and documented with a written consent form *[Complete Sections 5.2 and 5.6]***

☒ **Implied or verbal consent will be obtained – subjects will not sign a consent form (waiver of written documentation of consent) *[Complete Sections 5.2, 5.3 and 5.6]***

☐ **Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception). *[Complete section 5.2, 5.4 and 5.6]***

☒ **Informed consent will not be obtained – request to completely waive the informed consent requirement. *[Complete Section 5.5]***

5.2 Obtaining Informed Consent

5.2.1 Timing and Location of Consent

Describe where and when the consent process will take place.

Procedure for the live cases:

Phase 1 of the consent happens by telephone or in person. This will be done using the Verbal Description Script. This will usually happen by telephone. Rarely, a potential participant will have a clinic visit scheduled, in which case a study coordinator will come in-person to review the Verbal Description Script.

Phase 2 of the consent process is the review and signing of the written consent form, and happens in person, typically on the day of the bronchoscopy in Same Day Admissions suite. A copy of the signed consent form is provided to the participant and is placed in the working folder by the research team and communicated to the clinical bronchoscopy team using a secure communications system (TigerText). TigerText is a secure texting platform that allows the secure communication of patient information between those authorized to see it. The verification of the signed consent is performed as the pre-procedure review performed by the clinical team in the bronchoscopy suite.

Procedure for the historical controls:

A full waiver of consent is requested for this portion of the study because participants will not be contacted (see rationale in Section 5.5.1) and medical record information will be extracted.

5.2.2 Coercion or Undue Influence during Consent

Describe the steps that will be taken to minimize the possibility of coercion or undue influence in the consent process.

The two phased approach is intended to minimize coercion or undue influence during the consent process. Participants are able to ask questions of their participation during the consent process on a day in advance of the day of their bronchoscopy.

Dr. Higgins and Penn State have financial interests in Broncus Medical, Inc. These financial interests have been reviewed by the University's Institutional and Individual Conflict of Interest Committees and are currently being managed by the University and reported to the NIH. As

mandated by Penn State's Office of Research Protections and stipulated in Dr. Higgins's conflict of interest management plan (Morgan Rhinehart, COI Monitor) dated 1 September 2022, Dr. Higgins will not be involved in consenting patients.

5.3 Waiver of Written Documentation of Consent

Review "HRP – 411 – Checklist – Waiver of Written Documentation of Consent."

5.3.1 Indicate which of the following conditions applies to this research:

☒ The research presents no more that minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

OR

☐ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. (*Note: This condition is not applicable for FDA-regulated research. If this category is chosen, include copies of a consent form and /or parental permission form for participants who want written documentation linking them to the research.)*

OR

☐ If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. (*Note: This condition is not applicable for FDA-regulated research.)*

Describe the alternative mechanism for documenting that informed consent was obtained:

[Type protocol text here]

5.3.2 Indicate what materials, if any, will be used to inform potential subjects about the research (e.g., a letter accompanying a questionnaire, verbal script, or implied consent form)

See verbal phone script.

5.4 Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

5.4.1 Indicate the elements of informed consent to be omitted or altered

Not applicable.

5.4.2 Indicate why the research could not practicably be carried out without the omission or alteration of consent elements

Not applicable.

5.4.3 Describe why the research involves no more than minimal risk to subjects.

Not applicable.

5.4.4 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

Not applicable.

5.4.5 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

Not applicable.

5.4.6 Debriefing

Explain whether and how subjects will be debriefed after participation in the study. If subjects will not be debriefed, provide a justification for not doing so. Add any debriefing materials to the study in CATS IRB.

Not applicable.

5.5 Informed consent will not be obtained – request to completely waive the informed consent requirement

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

5.5.1 Indicate why the research could not practicably be carried out without the waiver of consent

Waiver of consent is being requested for the historical controls only.

The historical controls consist of persons who previously underwent clinical bronchoscopy from 2017-2022.They were referred for the bronchoscopy but typically have been sent back for care by a different physician. Therefore, they are likely not being seen by the Pulmonary or Thoracic Surgery service and consent would not be able to be obtained. Also, there is a high fatality rate for persons diagnosed with lung cancer, and for the integrity of the study we would not want to exclude individuals who have died.

5.5.2 Describe why the research involves no more than minimal risk to subjects.

The data collected for the historical control group consists of chart review only.

5.5.3 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

The data collected for the historical control group consists of chart review only.
Efforts to protect privacy are outlined below.

5.5.4 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

The data collected for the historical control group includes clinical information from the medical record including linking the bronchoscopy results and the pathologic samples; this requires knowledge of the identity of the historical cases.

5.5.5 Additional pertinent information after participation

Explain if subjects will be provided with additional pertinent information after participation. If not applicable, indicate "not applicable."

Not applicable.

5.6 Consent – Other Considerations

5.6.1 Non-English-Speaking Subjects

Indicate what language(s) other than English are understood by prospective subjects or representatives.

If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Indicate whether the consent process will be documented in writing with the long form of the consent documentation or with the short form of the consent documentation. Review "HRP-091 –SOP- Written Documentation of Consent" and "HRP-103 -Investigator Manual" to ensure that you have provided sufficient information.

This study will not be enrolling non-English speaking subjects. The Verbal Description Script is the verbal consent form, and that is not translated. Additionally, this study does not offer benefits to the subjects.

5.6.2 Cognitively Impaired Adults

Refer "HRP-417 -CHECKLIST- Cognitively Impaired Adults" for information about research involving cognitively impaired adults as subjects.

5.6.2.1 Capability of Providing Consent

Describe the process to determine whether an individual is capable of consent.

Not applicable.

5.6.2.2 Adults Unable to Consent

Describe whether and how informed consent will be obtained from the legally authorized representative. Describe who will be allowed to provide informed consent. Describe the process used to determine these individual's authority to consent to research.

For research conducted in the state of Pennsylvania, review "HRP-013 -SOP- Legally Authorized Representatives, Children and Guardians" to be aware of which individuals in the state of Pennsylvania meet the definition of "legally authorized representative."

For research conducted outside of the state of Pennsylvania, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "HRP-013 - SOP- Legally Authorized Representatives, Children, and Guardians."

Not applicable.

5.6.2.3 Assent of Adults Unable to Consent

Describe the process for assent of the subjects. Indicate whether assent will be required of all, some or none of the subjects. If some, indicate which subjects will be required to assent and which will not.

If assent will not be obtained from some or all subjects, provide an explanation of why not.

Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.

Not applicable.

5.6.3 Subjects who are not yet adults (infants, children, teenagers)

5.6.3.1 Parental Permission

Describe whether and how parental permission will be obtained. If permission will be obtained from individuals other than parents, describe who will be allowed to

provide permission. Describe the process used to determine these individual's authority to consent to each child's general medical care.

For research conducted in the state of Pennsylvania, review "HRP-013-SOP- Legally Authorized Representatives, Children and Guardians" to be aware of which individuals in the state of Pennsylvania meet the definition of "children."

For research conducted outside of the state of Pennsylvania, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "HRP-013-SOP- Legally Authorized Representatives, Children, and Guardians."

Not applicable.

5.6.3.2 Assent of subjects who are not yet adults

Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent. When assent of children is obtained describe whether and how it will be documented.

Not applicable.

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

This section is about the access, use or disclosure of Protected Health Information (PHI). PHI is individually identifiable health information (i.e., health information containing one or more 18 identifiers) that is transmitted or maintained in any form or medium by a Covered Entity or its Business Associate. A Covered Entity is a health plan, a health care clearinghouse or health care provider who transmits health information in electronic form. See "HRP-103 -Investigator Manual" for a list of the 18 identifiers.

If requesting a waiver/alteration of HIPAA authorization, complete sections 6.2 and 6.3 in addition to section 6.1. The Privacy Rule permits waivers (or alterations) of authorization if the research meets certain conditions. Include only information that will be accessed with the waiver/alteration.

[Do not type here]

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☒ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Include the following statement as written – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable</u>.**

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Describe the plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research. Include when and how identifiers will be destroyed. If identifiers will be retained, provide the legal, health or research justification for retaining the identifiers.

Identifiers are destroyed as soon as a participant is determined to be ineligible or if the participant declines consent. We do not retain a screening list or identifiers for screening purposes.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Provide reasons why this research could not practicably be carried out without access to and use of PHI.

This is a study of people who are undergoing or have previously undergone clinical bronchoscopy for the purpose of lung cancer diagnosis and staging. Therefore, PHI is central to their care.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Provide reasons why this research could not practicably be carried out without the waiver or alternation of authorization.

For potential participants in the live case portion of the study, a full waiver is requested because the Phase 1 of the consent happens by telephone or in person. This allows the research images to be prepared without incurring a delay in the participant's clinical care; i.e., diagnosis of suspected lung cancer.

For potential participants in the live case portion of the study, a partial waiver is requested to access the medical record. Access to the medical record allows extraction of clinical diagnostic information such as CT interpretation and pathologic findings from clinical biopsies. In Phase 2 the participant will read and sign a written consent form and will be given a signed copy of the consent form in advance of using the research images during the clinical bronchoscopy.

We request a full waiver for the historical controls. As described in section 5.5.1, the historical controls consist of persons who previously underwent clinical bronchoscopy in 2017-2022. They were referred for the bronchoscopy but typically have been sent back for care by a different physician including other hospitals and healthcare systems.

6.3 Waiver or alteration of authorization statements of agreement

By submitting this study for review with a waiver of authorization, you agree to the following statement – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver or alteration of authorization. **If the section is not applicable, remove the statement and indicate as not applicable.**

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

Data collection materials that will be seen or used by subjects in your study must be uploaded to CATS IRB (http://irb.psu.edu). **DO NOT** include any actual data collection materials in this protocol (e.g., actual survey or interview questions)

[Do not type here]

7.1 Study Design

Describe and explain the study design.

This is a prospective study design with both a feasibility portion ("Aim 1") and case-control design ("Aims 2 & 3"). This corresponds with the human studies proposed in the funded NIH R01 grant 2R01-CA151433. In particular, the Aims of this protocol, as summarized in Section 1.1, align with the R01 application as follows:

1) Aim 1 corresponds to studies in Section C.2.3 Prospective Human Studies: Safety and Functionality
2) Aim 2 corresponds to studies in Section C.3.1 Peripheral Tumor Diagnosis
3) Aim 3 corresponds to studies in Section C.3.2 Central-Chest Lymph-Node Staging

The initial Aim 1 studies test the VN system for the first time within the complete clinical work flow during a clinical bronchoscopy. As such, we use a small case series to optimize the VN system.

As a result of the COVID pandemic, we have incurred associated delays in research. The pandemic has also increased the extent of the safety precautions imposed on research, making it more time-consuming to complete studies. In addition, the NIH grant has incurred significant cuts during its duration. Because of these factors, we have slightly modified the study design for Aims 2 and 3 from that described in the RO1 application. We are replacing a randomized case control design with a case series (consented clinical bronchoscopy cohort, i.e. "live cases") as compared with patients who have previously undergone a clinical bronchoscopy ("historical controls"). All other procedures are as described in the proposal. The NIH approved this change on 12 September 2022.

7.2 Study Procedures

Provide a step by step description of all research procedures being conducted (broken down by visit, if applicable) including such information as below (where and when applicable); describe the following:

- HOW: (e.g., data collection via interviews, focus groups, forms such as surveys and questionnaires, medical/school records, audio/video/digital recordings, photographs, EKG procedures, MRI, mobile devices such as electronic tablets/cell phones, observations, collection of specimens, experimental drug/device testing, manipulation of behavior/use of deception, computer games, etc.)
- WHERE: (e.g., classrooms, labs, internet/online, places of business, medical settings, public spaces, etc.)

Aim 1: Safety and Functionality Testing

The in-suite testing will be performed to assess safety and functionality only and will not be used for the full duration of the bronchoscopy procedure. Upon the completion of the Aim-1 study, the optimized VN system is now employed for the studies of Aims 2 and 3 for collection of primary and secondary endpoints.

Aim 2: Peripheral Tumor Diagnosis

The in-suite testing described above will be used for the full duration of the bronchoscopy procedure, until

All procedures are identical to those performed in Aim 1, with the exception that the optimized VN system may be used by the clinician for guidance, in addition to their other available standard clinical equipment.

Aim 3: Central-Chest Nodal Staging

All procedures are identical to those performed in Aim 1, with the exception that the optimized VN system may be used by the clinician for guidance, in addition to their other available standard clinical equipment.

As stated earlier, a lung-cancer patient often requires both a nodule diagnosis and nodal staging in the same bronchoscopic procedure. Thus, a consented patient could take part in both the Aim 2 and 3 procedures, depending on the clinical indications and procedure-time limitations. This will be determined by the treating clinician as per standard of care. Yet, even though the guidance process – be it for peripheral nodule diagnosis or central-chest lymph-node staging – is known to typically take approximately 10-15 minutes, the physician may decide that the available time only affords perform one of the tests.

Study procedures are performed for participants in Aims 1-3 as indicated in the table below. A description of each study procedure is provided in sections 7.2.1-7.2.3

		Aim 1	Aim 2	Aim 3
5.2.1	**Verbal Consent**	X	X	X
7.2.1	**Pre-Bronchoscopy Procedures**	X	X	X
5.2.1	**Written Consent**	X	X	X
7.2.2	**In-OR/Bronchoscopy Suite Use**	X	X	X
7.2.3	**Safety and Functionality Testing**	X		
7.2.4	**Guidance to Peripheral Nodules/Tumors**		X	
7.2.5	**Guidance to Central Chest Lymph Nodes**			X
7.2.6	**Post-Bronchoscopy Procedures**	X	X	X
7.2.7	**Historical Controls**		X	X

7.2.1 Pre-Bronchoscopy Procedures

Provide a description of what procedures will be performed on visit 1 or day 1 or pre-test in order of how these will be done. If your study only involves one session or visit, use this section only and indicate 7.2.2 as not applicable.

For each potential enrolled patient, the clinical CT scan and PET scan (if available) will be viewed by the technical team to determine whether or not it meets technical criteria. If it does, the clinician will be notified and determine whether to proceed with contacting the patient to explain the protocol and obtain verbal consent.

Upon receiving verbal consent, the technical team acquires a redacted radiology report provided by the radiologist. The technical team then uses established software tools to anonymize the imaging scans, as described in the manual entitled "The Virtual Navigator (VNS) Project" in Sect. 5.3.1. Continuing, the technical team next use the anonymized scans, the redacted radiology report, and indications from the bronchoscopist to build a procedure plan. Software methods are used to build the plan. The procedure plan consists of the following:

a) A set of data loaded into the Virtual Navigator system for previewing the plan and for guiding the live bronchoscopy. These data include definitions of the clinical sites of interest, airway pathways leading to each site, and, possibly, suggested bronchoscope maneuvers at key points along each pathway.
b) A hard-copy summary of the procedure plan, which gives a series of pictures that illustrate the pathway through airways leading to each site of interest.
c) A movie (video file) of each computed pathway leading to each site of interest.

7.2.2 In-Suite/OR Testing

Provide a description of what procedures will be performed on visit 2 or day 2 or post-test in order of how these will be done. If your study involves more than two sessions or visits replicate this section for each additional session or visit (e.g., 7.2.3, 7.2.4, etc.).

In the operating room (OR), the Virtual Navigator guidance computer is interfaced to the bronchoscopy hardware to tap off the live bronchoscopy and EBUS video feeds. The standard OR medical team (technicians, clinical fellows, et al.) is on hand, and standard clinical facilities

(e.g., fluoroscopy, CT/PET image viewer) are available. Our technical team is also present to record all computer display information. They also operate the guidance computer during the guided procedure and offer any assistance in case of unanticipated issues. The participant's clinical bronchoscopy video will be recorded by the radiology imaging management system (contact: Matthew Bechtel, MB HG517, ext. 289316).

Prior to performing the procedure, the attending bronchoscopist reviews the procedure plan, built earlier during the Pre-Bronchoscopy Procedures (Sect. 7.2.1), on either the guidance computer or iPad tablet PC. The preview allows the bronchoscopist to view a simulated bronchoscopy with guidance to the lesions they will be seeking.

7.2.3 Safety and Functionality Testing

The safety and functionality of the VNS will be validated and optimized during live bronchoscopy procedures (dry-run cases). To do this, we will observe the VN system's functionality during the study (Does it crash? Is it too slow? Are there errors?), we will note how the mobile computer fits into the surgical suite's set-up (Do we need to move the computer to a different location?), and we note physician feedback on the system (Are the presented images clear? Too small? Superfluous? Does the physician find them useful?). In addition, we record all data from each study and use these data to note other observations. Based on this information, system- and work-flow modifications will be made to improve the system.

7.2.4 Guidance to Peripheral Nodules/Tumors

The bronchoscopist then undertakes bronchoscopic diagnosis and/or staging, guided by their standard clinically available data sources (bronchoscopic video, clinical images) and also by the supplemental images provided on the guidance computer's display. This does not introduce energy into the subject. During the bronchoscopic procedure, the bronchoscopist will be able to view the guiding images and to act on them using standard clinical practice. These images include:

a) 3D CT-rendered airway tree, depicting the airway guidance route, current location, and clinical site of interest (peripheral nodule)
b) Registered live video-bronchoscope view and corresponding CT-based virtual bronchoscope view, where the virtual bronchoscope view also depicts the guidance route, location of site of interest, and distance to site
c) Registered real EBUS view and CT-based virtual EBUS view, with indication of site of interest's location
d) Guidance instructions; e.g., Move forward (indicates move the bronchoscope forward); Rotate Clockwise (indicates rotate the bronchoscope clockwise).

During the procedure, then bronchoscopist maneuvers the bronchoscope to localize and possibly biopsy each clinical site of interest, as is standard clinical practice. Any biopsies that are taken are handled and processed according to medically established diagnostic procedures as is standard of care. Performance of the clinical pathologic interpretation is outside of the scope of this protocol. After the guided procedure is completed, all recordings are saved. The technical team shuts down the guidance computer. Post-procedure work then occurs (Section 7.2.6).

7.2.5 Guidance to Central Chest Lymph Nodes

The bronchoscopist then undertakes bronchoscopic diagnosis and/or staging, guided by their standard clinically available data sources (bronchoscopic video, clinical images) and also by the supplemental images provided on the guidance computer's display. This does not introduce energy into the subject. During the bronchoscopic procedure, the bronchoscopist will be able to view the guiding images and to act on them using standard clinical practice. These images include:

a) 3D CT-rendered airway tree, depicting the airway guidance route, current location, and clinical site of interest (central chest lymph nodes)
b) Registered live video-bronchoscope view and corresponding CT-based virtual bronchoscope view, where the virtual bronchoscope view also depicts the guidance route, location of site of interest, and distance to site
c) Registered real EBUS view and CT-based virtual EBUS view, with indication of site of interest's location
d) Guidance instructions; e.g., Move forward (indicates move the bronchoscope forward); Rotate Clockwise (indicates rotate the bronchoscope clockwise).

During the procedure, then bronchoscopist maneuvers the bronchoscope to localize and possibly biopsy each clinical site of interest, as is standard clinical practice. Any biopsies that are taken are handled and processed according to medically established diagnostic procedures as is standard of care. Performance of the clinical pathologic interpretation is outside of the scope of this protocol. After the guided procedure is completed, all recordings are saved. The technical team shuts down the guidance computer. Post-procedure work then occurs (Section 7.2.6).

7.2.6 Post-Bronchoscopy Procedures

Aim 1: Upon completion of the bronchoscopy, radiology imaging services (Matthew Bechtel) is notified so that the recorded procedure images can be transferred to a server accessible by the technical team. Also, all data recorded by the technical team.

Based on observations from the recorded procedure data and guidance computer display, along with other observations noted by the research team during the procedure, the technical team makes the appropriate system modifications. These include computer software bug fixes and computer display updates. Also, work-flow procedural adjustments are made.

Aim 2: Bronchoscopy records will be reviewed including the indication and CT scan to determine the presence of peripheral lesions. We will review the procedure notes and pathology reports to determine diagnostic yield (primary outcome), the number of biopsy samples per tumor; diagnosis (malignant, non-malignant, indeterminate); complications (e.g., pneumothorax); the distance of a biopsy location from computed optimal biopsy site; and procedure time (total and per tumor).

Aim 3: Bronchoscopy records will be reviewed, including the indication and CT scan, to determine the presence of central chest lymph nodes. We will review the procedure note and pathology reports to determine the number of nodal stations biopsied (primary outcome) and the diagnostic yield (diagnosis made by TBNA), number of biopsies per lymph node, adequacy of biopsy samples, complications; distance of a biopsy site from the computed optimal biopsy site, procedure time (total and per node) (secondary outcomes).

7.2.7 Historical Controls

The historical controls will be identified by review of the bronchoscopy schedule for the period starting 7/1/2017 through 06/30/2022. Cases will be those individuals ages 18 and over who underwent a clinical bronchoscopy to evaluate abnormal lung parenchyma and/or central chest lymph nodes and who also have had a pre-bronchoscopy clinical CT scan with a clinical interpretation in the medical record. The cases will begin with the most recent case and work backwards sequentially until the target sample size has been accrued.

For each historical control, the technical team will be provided with demographic information (e.g. age, diagnosis, date of CT scan, date of PET scan, gender). A redacted radiology report, a bronchoscopy procedure note, and redacted pathology report will also be provided.

Aim 2: Bronchoscopy reports will be reviewed from historical controls who had a bronchoscopy performed for suspected lung cancer, and have a CT scan with a radiology report in their records. We will review the procedure notes and pathology reports to determine diagnostic yield (primary outcome), the number of biopsy samples per tumor; diagnosis (malignant, non-malignant, indeterminate); complications (e.g., pneumothorax); the distance of a biopsy location from computed optimal biopsy site; procedure time (total and per tumor); and the number of passes per procedure (secondary outcomes).

Aim 3: Bronchoscopy reports will be reviewed from historical controls who had a bronchoscopy performed for suspected lung cancer, and have a CT scan with a radiology report in their records. We will review the procedure note and pathology reports to determine the number of nodal stations biopsied (primary outcome) and the diagnostic yield (diagnosis made by TBNA), number of biopsies per lymph node, adequacy of biopsy samples, complications; distance of a biopsy site from the computed optimal biopsy site, procedure time (total and per node) (secondary outcomes).

7.3 Duration of Participation

Describe how long subjects will be involved in this research study. Include the number of sessions and the duration of each session - consider the total number of minutes, hours, days, months, years, etc.

Participant's direct participation will include the consent process (verbal and in-person) and the research portion of the bronchoscopy, which is embedded within the clinical diagnostic bronchoscopy. The verbal portion of the consent precedes the in-person consent and bronchoscopy by typically 3 to 10 days. The in-person consent and bronchoscopy typically take place on the same day.

The derived images and materials will be used indefinitely.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Provide a brief description of all test articles (drugs (including any foods and dietary supplements), devices and/or biologics used in the research including the purpose of their use and their approval status with the Food and Drug Administration (FDA). Include information about the form of the drug product (e.g., tablets, capsules, liquid).

The Virtual Navigator is a device that meets the FDA requirements for an IDE Exemption for a diagnostic device, as detailed below.

The Virtual Navigator is a software package that runs on a mobile Windows-based computer. The computer takes in up to four clinical image/video sources, ordered by the clinician for clinical purposes, as listed below:

i. 3D CT (computed tomography) imaging scan
ii. 3D PET (positron emission tomography) imaging scan (optional)
iii. Bronchoscopic video of the airway tree interior (either live or recorded)

iv. Ultrasound video of scanned anatomy outside the airways, as provided by an endobronchial ultrasound (EBUS) probe [used in tandem with the bronchoscope] (optional)

Regarding the input clinical images above, a 3D imaging scan is a stack of 2D images that depict a scanned portion of a patient's anatomy. Also, a video consists of a time series of 2D images that depict either the illuminated airway tree interior (provided by the bronchoscope) or scanned exterior anatomy (provided by the EBUS probe).

The Virtual Navigator provide images that aid in:

a) Visualizing graphical images, based on clinical images ordered by the clinician for clinical purposes.
b) Planning a bronchoscopic procedure
   i. A graphical report and a movie – both representing the plan – can be viewed
   ii. The plan facilitates live image computation during a guided bronchoscopy procedure
c) Presenting images that assist with guiding a bronchoscopic procedure
   i. Graphical images are presented during the clinical procedure that suggest how the physician/bronchoscopist could conceivably deploy and maneuver the bronchoscope and EBUS more effectively.

The device is therefore used for diagnostic purposes. However, it is not used as a diagnostic procedure without confirmation by another, medically established product or procedure (i.e., bronchoscopy with possible tissue sampling). Note that the physician/bronchoscopist always decides how to maneuver and deploy the devices (bronchoscope and EBUS). Also,

a) The physician/bronchoscopist can ignore the presented images at any time. In fact, the physician/bronchoscopist can ask that the computer be shut off at any time.
b) The physician/bronchoscopist chooses when to do tissue sampling, if ever, based on clinical indications only. The research protocol does not include the collection of tissue samples. The results from clinically indicated samples may be reviewed. The testing procedure is therefore noninvasive.
c) All standard clinical image/video sources, listed above, along with other standard clinical records and devices, are always available to the physician/bronchoscopist during a procedure.

Thus, the Virtual Navigator does not alter, limit, or impede the standard clinical procedures or operating room lay-out (equipment) in any way. In other words, it does not require an invasive sampling procedure that presents significant risk.

The research images produced by the Virtual Navigator system are presented on the guidance computer screen, placed adjacent to the clinical images that are part of the standard of care. This does not introduce energy into the subject. At no time do the research images obscure the clinical images. The clinical images include CT and, possibly, PET scans, presented in axial, coronal, and sagittal planes at the discretion of the clinician. The clinical images also include real-time bronchoscopic video displayed on a clinical monitor mounted above the patient, along with EBUS video, if EBUS is used.

7.4.2 Treatment Regimen

Describe dose, route of administration and treatment duration. Include information about dose adjustments.

Not applicable.

7.4.3 Method for Assigning Subject to Treatment Groups

Describe the randomization process and how the associated treatment assignment will be made.

Not applicable.

7.4.4 Subject Compliance Monitoring

Insert the procedures for monitoring subject compliance.

Not applicable.

7.4.5 Blinding of the Test Article

Describe how the test article is blinded.

Not applicable.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

Describe how the test article will be obtained and from what source. Describe how the study test article will be packaged along with amounts (e.g., number of tablets/capsules or volume of liquid) and labeling. If drug kits are used, describe all the contents of the kit and associated labeling.

The Virtual Navigator software system (test article) is by viewed by the bronchoscopist during the procedure in the OR as noted above. Clinical images are uploaded on the research server for viewing during pre-bronchoscopy procedures. Upon verbal consent the image is de-identified and transferred to MIPL for pre-bronchoscopy processing. Research images are coded with a participant number and do not have identifying information.

Research images are presented during the bronchoscopy on the Virtual Navigator and available for reviewing in advance of the procedure. The images are displayed on a research computer, which is brought into the bronchoscopy suite (and has been cleared by Biomedical Engineering for use in the OR).

7.4.6.2 Storage

Describe the plans to store, handle the test article so they will be used only on subjects and only by authorized investigators. Describe storage temperature requirements and how temperature will be monitored and recorded.

The research computer containing the Virtual Navigator software package is stored in Dr. Bascom's research laboratory (Room C6627 in the Penn State College of Medicine). The research images are uploaded to the research computer for the purposes of the procedure and then removed.

7.4.6.3 Preparation and Dispensing

Describe how the test article will be assigned to each subject and dispensed. Describe the steps necessary to prepare the test article. Include where the test article preparation will be done and by whom. Fully describe how the study treatment is to be administered and by whom.

All subjects included in the consented cohort will assigned to receive the device (software package images). The research images are coded with the subject number and do not include PHI. Redacted, clinical image interpretations are included in the research dataset provided to MIPL.

7.4.6.4 Return or Destruction of the Test Article

Describe the procedures for final reconciliation of the test article supply at the end of the study and whether the test article is to be shipped back to a source or destroyed on site.

The Virtual Navigator software package will not be destroyed. Coded research images produced by the software package are stored at MIPL for additional analysis.

7.4.6.5 Prior and Concomitant Therapy

Describe what prior and/or concomitant medical therapy will be collected. Describe which concomitant medicines/therapies are permitted during the study. Describe which concomitant medicines are not permitted during the study.

All concomitant medicines or therapies used for standard of care are permitted during the study.

8.0 Number of Subject and Statistical Plan

8.1 Number of Subjects

Indicate the maximum number of subjects to be accrued/enrolled. Distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures if applicable (i.e., numbers of subjects excluding screen failures.)

We request a total of 166 subjects to be enrolled. Eighty-six of these subjects will be a part of the consented clinical bronchoscopy cohort and 80 will be historical controls. Our previous experience in study design indicates there will not be screen fails or drop-outs.

8.2 Sample size determination

If applicable, provide a justification of the sample size outlined in section 8.1 to include reflections on, or calculations of, the power of the study.

Aim 1: the sample size of 6 subjects is based on research clinic experience of standing up new systems

Aim 2: The sample size of 112 is based on the following: 1) reported diagnostic yield by state-of-the-art practice = 60% (controls); 2) hypothesized yield using our system = 85%.

Aim 3: The sample size of 48 is based on the following: 1) the number of nodes biopsied during a staging bronchoscopy in state-of-the-art practice = 3 (controls) 2) hypothesized number of nodes biopsied using our system = 7.

8.3 Statistical methods

Describe the statistical methods (or non-statistical methods of analysis) that will be employed.

Aim 1: Not applicable. These studies focus on assessing basic VN system functionality and noting/correcting workflow issues, as discussed earlier.

Aim 2: We apply Fisher's exact test to compare the two groups (cases and historic controls) with respect to the binary outcome of a positive diagnostic yield, giving a test with statistical power = 0.80 via a two-sided, 0.05 significance level test.

Aim 3: We apply ordinal logistic regression to compare the two groups (cases and historic controls) with respect to the ordinal outcome of the number of nodes biopsied, giving a test with statistical power = 0.90 via a two-sided, 0.05 significance level test. We expect a high percentage of patients with early-stage disease (or no disease!). Late-stage patients, however, likely require < 3 stations to reach a confirmed staging decision. While this could skew the mean number of stations considered downward, it does not affect diagnostic yield, the prime clinical goal.

9.0 Data and Safety Monitoring Plan

This section is required when research involves more than Minimal Risk to subjects as defined in "HRP-001 SOP- Definitions."

Minimal Risk is defined as the probability and magnitude of harm or discomfort anticipated in the research that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For research involving prisoners, Minimal Risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Please complete the sections below if the research involves more than minimal risk to subjects, otherwise indicate each section as not applicable.

[Do not type here]

9.1 Periodic evaluation of data

Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Not applicable.

9.2 Data that are reviewed

Describe the data that are reviewed, including safety data, untoward events, and efficacy data.

Not applicable.

9.3 Method of collection of safety information

Describe the method by which the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls and with subjects).

Not applicable.

9.4 Frequency of data collection

Describe the frequency of data collection, including when safety data collection starts.

Not applicable.

9.5 Individuals reviewing the data

Identify the individuals who will review the data. The plan might include establishing a data and safety monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

Not applicable.

9.6 Frequency of review of cumulative data

Describe the frequency or periodicity of review of cumulative data.

Not applicable.

9.7 Statistical tests

Describe the statistical tests for analyzing the safety data to determine whether harms are occurring.

Not applicable.

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9.8 Suspension of research

Describe any conditions that trigger an immediate suspension of research.

Not applicable.

10.0 Risks

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration and reversibility of the risks. Consider all types of risk including physical, psychological, social, legal, and economic risks. Note: Loss of confidentiality is a potential risk when conducting human subject research.

- If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.
- If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.
- If applicable, describe risks to others who are not subjects.

There are risks to the clinical procedures performed. These risks are disclosed as part of the clinical consenting process.

This research is minimal risk. There is no additional physical risk to the patient because all procedures will be performed for clinical indications. The bronchoscopist will use the research images in their clinical decision making during the procedure. There is a possibility that the bronchoscopist may perform a biopsy for clinical purposes that they may not have otherwise performed because of information they receive from the research images. In our nearly 20 years of experience of live guided bronchoscopies, we have not had any adverse events attributable to the presence of research images during clinical bronchoscopy procedures.

Risks to privacy are addressed by having a linking list that is on a research server with access limited to study personnel. There will not be individually identifiable information on spread sheets, abstracts or published reports.

There is a potential loss of confidentiality that is minimized through the preparation of a de-identified, linked research database. There is no financial risk for participation because the Hershey Medical Center Outpatient Access and Scheduling (OPAS) system receives pre-authorization for the clinical diagnostic studies.

11.0 Potential Benefits to Subjects and Others

11.1 Potential Benefits to Subjects

Describe the potential benefits that individual subjects may experience from taking part in the research. If there is no direct benefit to subjects, indicate as such. Compensation is not considered a benefit. Compensation should be addressed in section 14.0.

There will be no direct benefit of the research to research participants. Our hypothesis is that this approach improves diagnostic yield; this has not been established.

11.2 Potential Benefits to Others

Include benefits to society or others.

There will be a future benefit to others if the research is successful. Primary beneficiaries will be future patients with lung cancer and other patients requiring bronchoscopy for nonmalignant conditions.

12.0 Sharing Results with Subjects

Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how information will be shared.

Results will not be shared with subjects.

13.0 Subject Payment and/or Travel Reimbursements

Describe the amount, type (cash, check, gift card, other) and timing of any subject payment or travel reimbursement. If there is **no** subject payment or travel reimbursement, indicate as not applicable.

Extra or Course Credit: Describe the amount of credit **and** the available alternatives. Alternatives should be equal in time and effort to the amount of course or extra credit offered. It is not acceptable to indicate that the amount of credit is to be determined or at the discretion of the instructor of the course.

Approved Subject Pool: Indicate which approved subject pool will be used; include in response below that course credit will be given and alternatives will be offered as per the approved subject pool procedures.

Not applicable.

14.0 Economic Burden to Subjects

14.1 Costs

Describe any costs that subjects may be responsible for because of participation in the research.

Subjects will not be responsible for any costs outside of costs related to their standard of care.

14.2 Compensation for research-related injury

If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

If there is no sponsor agreement that addresses compensation for medical care for research subjects with a research-related injury, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

For sponsored research studies with a research agreement with the sponsor that addresses compensation for medical care for research-related injuries, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Such charges may be paid by the study sponsor as outlined in the research agreement and explained in the consent form.

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

15.0 Resources Available

15.1 Facilities and locations

Identify and describe the facilities, sites and locations where recruitment and study procedures will be performed.

If research will be conducted outside the United States, describe site-specific regulations or customs affecting the research, and describe the process for obtaining local ethical review. Also, describe the

principal investigator's experience conducting research at these locations and familiarity with local culture.

MIPL Laboratory:
Dr. Higgins is Director of the Multidimensional Image Processing Laboratory (MIPL, 204 Electrical Engineering West). The laboratory is a 750 sq. ft. facility, housing various computer facilities, research-only bronchoscopes, a dedicated radiology data server, human airway-tree phantoms, camera calibration facilities, and other devices. On the order of ten graduate students and University Honors students work in the laboratory. Research focuses on the area of 3D/4D radiological image analysis and visualization, with particular emphasis on methods for image-guided intervention systems for the chest, virtual endoscopy, video processing and calibration, data fusion, image segmentation, visualization, filtering, and related areas. Information on laboratory staff and publications can be accessed on the World Wide Web at http://www.mipl.ee.psu.edu.

Dr. Bascom's Offices:
Dr. Bascom's research offices are located in Suite 5301 of the Academic Support Building. She also has a space in room C6627 in the College of Medicine. The offices have computer facilities and related equipment for research in pulmonary disorders. They accommodate postdoctoral fellows, graduate students, a research technician, and clinical research fellows. Research focuses on studies in bronchoscopy, lung-cancer pathology, pulmonary imaging, and epidemiology studies.

Clinical Facilities:
a) The Department of Radiology has an extensive range of imaging facilities for whole-body imaging, including facilities for CT, MRI, ultrasound, nuclear medicine, breast imaging, angiography, analysis workstations, and PACS. Relevant to this project are the following:

1. One Siemens Definition Flash 128-slice dual-tube 3D MDCT scanner
2. One Siemens Definition 64-slice dual-tube 3D MDCT scanner
3. One Siemens Sensation 40-slice 3D MDCT scanner + CT fluoroscopy (CareVision)
4. One Siemens Sensation 40-slice 3D MDCT scanner
5. One Siemens Sensation 16-slice 3D MDCT scanner + CT fluoroscopy (CareVision)
6. Philips TrueFlight Gemini Integrated PET/CT scanner
7. Siemens Biograph mCT 20 (Large Bore, Time of Flight, HD package) PET/CT scanner

b) Bronchoscopy and Interventional Pulmonology has a wide range of state-of-the-art devices, including 36 bronchoscopes, associated video processors and light sources, ultrasound centers, and DVR video recorder for various purposes. Among these are:

1. Two Olympus BF-MP160F 4.0-mm-diameter videobronchoscopes
2. Olympus P260F 4.0-mm-diameter HD videobronchoscope
3. Five Olympus integrated BF-UC180F CP-EBUS bronchoscopes (endobronchial ultrasound and power Doppler)
4. Olympus radial-probe UM-S20-17S RP-EBUS
5. Olympus 4.1-mm-diameter BF-P190 and two BF-1T180 bronchoscopes, enabling narrowband imaging (through Exera III CV-190 video processor)
6. Two Olympus BF-P60 bronchoscopes, equipped with auto-fluorescence imaging
7. Olympus BF-P190, two BF-Q180 bronchoscopes, and Olympus P260F videobronchoscope, for narrowband imaging (through Exera III CV-190 video processor)
8. Olympus EXERA III CV-190 video center and CLV-190 light source for HD imaging
9. Novadaq/Xillix Onco-LIFE light source and video camera for autofluorescence bronchoscopy.

c) The Operating Room suite dedicated to pulmonary procedures has the following IGI navigational bronchoscopy systems:

1. Broncus LungPoint Virtual Bronchoscopic Navigation System

2. Veran SPiN Thoracic Navigation System

d) Radiation Oncology – In association with the PSCI, the department has (among other units):
1. Two Varian Triology radiation therapy units, equipped with real-time conebeam CT
2. GammaKnife radiosurgery system

e) Cardiothoracic surgery – A full array of surgical facilities for video-assisted thoracic surgery (VATS), thoracotomy, and other care facilities are available.

f) Penn State Cancer Institute (PSCI) – PSCI is a 175,000 sq. ft. multidisciplinary facility dedicated to cancer research and state-of-the-art patient care. Clinical departments within the College of Medicine (Radiology, Pulmonary and Critical Care Medicine, Cardiothoracic Surgery, Radiation Oncology, Pathology) are coordinated in activities through PSCI.

15.2 Feasibility of recruiting the required number of subjects

Indicate the number of potential subjects to which the study team has access. Indicate the percentage of those potential subjects needed for recruitment.

The clinical bronchoscopy service that serves the thoracic oncology program at Penn State Hershey Medical Center will complete an estimated 240 eligible bronchoscopies for calendar year 2022, based on first quarter volumes. We anticipate completing this protocol over a two year period, enrolling 88 participants prospectively. The recruitment efficiency needed to complete the protocol is thus 88/480 = 18%. This is a volume that is realistic based on prior experience.

15.3 PI Time devoted to conducting the research

Describe how the PI will ensure that a sufficient amount of time will be devoted to conducting and completing the research. Please consider outside responsibilities as well as other on-going research for which the PI is responsible.

Drs. Higgins and Bascom meet regularly for the development of this application, and continue to meet to assure smooth implementation.

15.4 Availability of medical or psychological resources

Describe the availability of medical or psychological resources that subjects might need as a result of their participation in the study, if applicable.

Not applicable.

15.5 Process for informing Study Team

Describe the training plans to ensure members of the research team are informed about the protocol and their duties, if applicable.

Weekly study coordinator and graduate student meetings will be the site of orientation and training.

16.0 Other Approvals

16.1 Other Approvals from External Entities

Describe any approvals that will be obtained prior to commencing the research (e.g., from engaged cooperating institutions IRBs who are also reviewing the research and other required review committees, community leaders, schools, research locations where research is to be conducted by the Penn State investigator, funding agencies, etc.).

Not applicable. No biopsies and no blood or tissue collection is done for the purpose of this study. Also, no radiology images are collected. Results of studies done as part of clinical care are reviewed.

16.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – **Penn State** Health **only** – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of "HRP-902 - Human Tissue For Research Form" in CATS IRB.

☐ Animal Care and Use – **All campuses** – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – **All campuses** – Research involves biohazardous materials (human biological specimens, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – **Penn State Health only** –Use of body fluids that had been collected for clinical purposes but are no longer needed for clinical use (remnant samples only).

☐ Clinical Research Center (CRC) Advisory Committee – **University Park** – Research involves the use of CRC services in any way.

☒ Conflict of Interest Review – **All campuses** – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – **Penn State Health only** – Research involves radiation procedures. After completion of coverage analysis by the Clinical Trials Office, all research involving radiation procedures (standard of care and/or research-related) requires upload of "HRP-903 - Radiation Review Form" in CATS IRB.

☐ IND/IDE Audit – **All campuses** – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – **Penn State Health only** – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Health Cancer Institute (PSCI) Protocol Review Committee or the PSCI Disease Team is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website.

☐ St. Joseph Administrative Review – **Penn State Health only** – Penn State Health Research that will involve St. Joseph Medical Center or St. Joseph Community Medical Groups, their patients, or their medical records.

17.0 Multi-Site Study

If this is a multi-site study (i.e., a study in which two or more institutions coordinate, with each institution completing all research activities outlined in a specific protocol) and the Penn State PI is the lead investigator, describe the processes to ensure communication among sites in the sections below.

[Do not type here]

17.1 Other sites

List the name and location of all other participating sites. Provide the name, qualifications and contact information for the principal investigator at each site and indicate which IRB will be reviewing the study at each site.

Not applicable.

17.2 Communication Plans

Describe the plan for regular communication between the overall study director and the other sites to ensure that all sites have the most current version of the protocol, consent document, etc. Describe the process to ensure all modifications have been communicated to sites. Describe the process to ensure that all required approvals have been obtained at each site (including approval by the site's IRB of record). Describe the process for communication of problems with the research, interim results and closure of the study.

Not applicable.

17.3 Data Submission and Security Plan

Describe the process and schedule for data submission and provide the data security plan for data collected from other sites. Describe the process to ensure all engaged participating sites will safeguard data as required by local information security policies.

Not applicable.

17.4 Subject Enrollment

Describe the procedures for coordination of subject enrollment and randomization for the overall project.

Not applicable.

17.5 Reporting of Adverse Events and New Information

Describe how adverse events and other information will be reported from the clinical sites to the overall study director. Provide the timeframe for this reporting.

Not applicable.

17.6 Audit and Monitoring Plans

Describe the process to ensure all local site investigators conduct the study appropriately. Describe any on-site auditing and monitoring plans for the study.

Not applicable.

18.0 Adverse Event Reporting

18.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

18.2 Recording of Adverse Events

Address the frequency and process for eliciting adverse event information from research subject, e.g., "Research subjects will be routinely questioned about adverse events at study visits."

In the response, incorporate the following as written:
All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

Adverse events will be elicited through review of the participants medical records as Drs. Higgins, Bascom and Toth, as well as the clinical bronchoscopist (if not Dr. Toth), look for any unanticipated outcomes following the procedures.

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study device will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

18.3 Causality and Severity Assessments

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

18.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

18.4.1 Written IND/IDE Safety Reports

For a drug study under an IND, incorporate the following from 21 CFR 312.32 as written – DO NOT ALTER OR DELETE:
The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

For a device study under an IDE, incorporate the following from 21 CFR 812.150 as written – DO NOT ALTER OR DELETE:
The Sponsor-Investigator will submit a completed FDA Form 3500Ato the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to all participating sub-investigators.

The completed FDA Form 3500Awill be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the Sponsor-Investigator first receives notice of the adverse effect.

If the results of the Sponsor-Investigator's follow-up evaluation show that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a completed FDA Form 3500Aas soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the Sponsor-Investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the Sponsor-Investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

Not applicable.

18.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

For a drug study under an IND, incorporate the following from 21 CFR 312.32 into the response, as written:
In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any unexpected, fatal or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

Not applicable.

18.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

18.6 Unblinding Procedures

Describe the procedures for unblinding study therapy on a subject, including documentation of this in the subject's source document. Include example(s) here why someone might unblind a study. In most cases, the unblinding will be part of managing a serious adverse reaction and will be reported with the serious adverse event. However, in cases where unblinding was not associated with a serious adverse event, such actions should be reported in a timely manner.

Not applicable.

18.7 Stopping Rules

In studies with a primary safety endpoint or studies with high risk to study subjects, provide the rules that define the circumstances and procedures for interrupting or stopping the study. If an independent Data and Safety Monitoring (DSMB) or Committee (DSMC) is set up for the study, the same stopping rules should be incorporated into the safety analysis plan as well.

The study will be paused if a serious, unanticipated and related event takes place and will be reported to the IRB. The study will then be terminated if deemed necessary by the IRB, NIH or investigators due to adverse events.

19.0 Study Monitoring, Auditing and Inspecting

19.1 Study Monitoring Plan

19.1.1 Quality Assurance and Quality Control

Include this section if FDA regulations apply to this study (see "WORKSHEET: Drugs (HRP-306)" and "WORKSHEET: Devices (HRP-307)". HRP-306 and HRP-307 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Describe how you will ensure that this study is conducted and that the data are generated, documented (recorded) and reported in compliance with this protocol, with institutional and IRB policies, with Good Clinical Practice guidelines and any other applicable regulatory requirements.

Indicate who is responsible for monitoring the conduct of the study and specify how often the study will be monitored.

For single-site studies with low risk, it may be appropriate for the principal investigator to monitor the study.

For multi-center studies or single site studies involving significant risk, an independent monitor may be required (e.g., monitoring by the staff of the PSU quality assurance program office(s) or by a clinical research organization).

Drs. Higgins and Bascom will monitor the study.

19.1.2 Safety Monitoring

Include this section if FDA regulations apply to this study (see "WORKSHEET: Drugs (HRP-306)" and "WORKSHEET: Devices (HRP-307)". HRP-306 and HRP-307 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Indicate the process for identifying, recording and reporting adverse events.

Specify roles for adverse event recording and monitoring. Indicate each staff member's role in the adverse event reporting process. Include the following if applicable:

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The **Research Coordinator** will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA and/or DSMB of all Unanticipated Problems/SAE's.

The **Monitor** will confirm that the AEs are correctly entered into the case report forms. The Monitor will also confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies as required.

Not applicable.

20.0 Future Undetermined Research: Data and Specimen Banking

If this study is collecting **identifiable** data and/or specimens that will be banked for future **undetermined research**, please describe this process in the sections below. This information should not conflict with information provided in section 22 regarding whether or not data and/or specimens will be associated with identifiers (directly or indirectly). If **NOT applicable**, indicate as such below in all sections.

[Do not type here]

20.1 Data and/or specimens being stored

Identify what data and/or specimens will be stored and the data associated with each specimen.

Anonymized data will be retained in the MIPL indefinitely.

20.2 Location of storage

Identify the location where the data and/or specimens will be stored.

Anonymized data will be stored at Dr. Higgins's MIPL lab; 204 Electrical Engineering West, University Park, PA

20.3 Duration of storage

Identify how long the data and/or specimens will be stored. If data and/or specimens will be stored indefinitely, indicate as such.

Anonymized data will be retained in the MIPL indefinitely.

20.4 Access to data and/or specimens

Identify who will have access to the data and/or specimens.

Approved IRB study team members, which include the research teams of Dr. Higgins and Dr. Bascom.

20.5 Procedures to release data or specimens

Describe the procedures to release the data and/or specimens, including: the process to request a release, approvals required for release, who can obtain data and/or specimens, and the data to be provided with the specimens.

Not applicable.

20.6 Process for returning results

Describe the process for returning results about the use of the data and/or specimens.

Not applicable.

21.0 References

List relevant references in the literature which highlight methods, controversies, and study outcomes.

Not applicable.

22.0 Confidentiality, Privacy and Data Management

IMPORTANT: The following section is required for all locations EXCEPT Penn State Health and the College of Medicine. Penn State Health and College of Medicine should skip this section and complete "HRP-598 Research Data Plan Review Form." In order to avoid redundancy, for this section state "See the Research Data Plan Review Form" if you are conducting Penn State Health research. Delete all other sub-sections of section 22.

See the Research Data Plan Review Form.