



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

Protocol Title:

Comparison of Lidocaine Administration during Flexible Bronchoscopy and Endobronchial Ultrasound: Topical vs Nebulized vs Atomized.

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Important Instructions for Using This Protocol Template:

1. Add this completed protocol template to your study in CATS IRB (<http://irb.psu.edu>) on the "Basic Information" page, item 7.
2. This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.
3. **Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.**
4. **For research being conducted at Penn State Hershey or by Penn State Hershey researchers only, delete the instructional boxes from the final version of the protocol prior to upload to CATS IRB (<http://irb.psu.edu>). For all other research, do not delete the instructional boxes from the final version of the protocol.**
5. When making revisions to this protocol as requested by the IRB, please follow the instructions outlined in the Study Submission Guide available in the Help Center in CATS IRB (<http://irb.psu.edu>) for using track changes.

If you need help...

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1. Objectives

1.1. Study Objectives

The purpose of this feasibility study is to use a multimodal approach of general anesthesia supplemented by topical analgesia during flexible bronchoscopy and endobronchial ultrasound. The aim is to determine if the administration of lidocaine via “spray as you go” vs. nebulizer would result in reduced severity of cough during the procedure and maximizing efficient sample acquisition while limiting the amount of general anesthetic given. The use of the vibrating mesh nebulizer is presumed to lead to an even distribution during lidocaine administration and thereby lead to decreased number of severe coughs during procedure improving efficiency of sample acquisition and reduce the dose of general anesthetic required.

1.2. Primary Study Endpoints

The primary endpoint will assess if different modes of lidocaine administration (“spray as you go” vs nebulized vs atomized) decrease the severity of intraoperative coughing. Severe coughs will be identified by the anesthesiologist and bronchoscopist as cough which results in pausing procedure and/or requiring repeated dosing of anesthetic.

1.3. Secondary Study Endpoints

Secondary endpoints will include: additional amount(s) of fentanyl and propofol used to suppress cough during procedure, cough and sore throat post-procedure and time to emergence following the end of the procedure.

2. Background

2.1. Scientific Background and Gaps

Flexible bronchoscopy and endobronchial ultrasound with transbronchial needle aspiration are the most commonly performed procedures by a pulmonologist when assessing lung disease, mediastinal and hilar lymphadenopathy. A combination of general anesthesia along with topical analgesia is important to maximize patient tolerance while limiting cough. The use of lidocaine as a topical anesthetic has the benefit of reducing the overall depth of the anesthetic with minimal risk of complications related to systemic absorption.

The current consensus statement on analgesia, anesthesia and sedation during bronchoscopy (Chest 2005) recommend sedation with Propofol which allows for shorter patient recovery, analgesia with Fentanyl due to its quick onset of action, rapid peak effect and relatively short duration of effect as well as topical anesthesia using lidocaine to provide the optimal environment for bronchoscopy while also limiting potential risks. Currently however, the optimal mode of administration of topical lidocaine has yet to be determined.

2.2. Previous Data

A previous study by Dreher, M., et al. published in Respiration evaluated nebulized versus “spray as you go” application of lidocaine during flexible bronchoscopy. This study selected patients undergoing diagnostic bronchoscopy with endobronchial or transbronchial biopsy. All patients underwent general anesthesia and intubation prior to procedure, then were randomized to a topical lidocaine versus Enk Fiberoptic Atomizer Set. Primary outcomes were the Aldrete score >9 to assess recovery after bronchoscopy and patient perceived tolerance with the visual analogue scale. This study showed no

difference between the two groups, however the primary outcome was patient comfort during procedure and most patients had complete amnesia for the procedure. Bronchoscopist and anesthesiologist evaluation of cough during procedure was not evaluated.

Another study by Stolz D., et al. published in Chest was a prospective, randomized, placebo controlled double blind trial which evaluated whether nebulized lidocaine provides additional benefit and reduces total anesthetic dose required during bronchoscopy in addition to topical lidocaine administration. Primary outcomes including both patient and operator visual analogue score for cough which were similar between groups. This however was not a comparison trial between different administration techniques of the lidocaine and included only flexible bronchoscopy patients, endobronchial ultrasound and biopsy patients were not included.

2.3. Study Rationale

While the procedures of flexible bronchoscopy and endobronchial ultrasound is commonly performed to assess a wide range of lung disease, studies evaluating the mode of administration of topical lidocaine to prevent coughing and improve efficiency of the procedure have not yet been completed. We propose a prospective, randomized, stratified sampling, open label study of topical vs nebulized vs atomized lidocaine during flexible bronchoscopy and endobronchial ultrasound. Postoperative outcome assessors will be blinded to intraoperative therapy. We propose to evaluate the different modes of administration of topical lidocaine and their effect on the number of severe coughs as per anesthesia and the bronchoscopist, total dosing of anesthesia, post-procedure cough and sore throat and complications related to lidocaine.

As there have been no studies in regards to the mode of lidocaine application in bronchoscopy, our study is a feasibility study to identify if a difference is present between nebulized and topical groups. If one is identified, we will plan to determine number needed to power a future superiority study.

3. Inclusion and Exclusion Criteria

3.1. Inclusion Criteria

The following inclusion criteria will be used:

1. Diagnosis of mediastinal and/or hilar lymphadenopathy requiring endobronchial ultrasound evaluation and transbronchial needle aspiration.
2. Diagnosis of pulmonary disease requiring flexible bronchoscopy
3. Greater than 18 years of age.

Vulnerable populations as identified in HRP-412, HRP-413, HRP-414, HRP-415, HRP-416 and HRP-417 will not be included in this study.

3.2. Exclusion Criteria

The following exclusion criteria will be used:

1. Any intervention beyond flexible bronchoscopy and EBUS/TBNA
2. Inability to tolerate bronchoscopy.
3. Patients that receive paralytics.
4. Patients with neuromuscular diseases.
5. Inability to consent for procedures.
6. Allergies to lidocaine or any other drugs used in protocol.
7. Existing renal insufficiency or liver disease

3.3. Early Withdrawal of Subjects

3.3.1. Criteria for removal from study

Withdrawn from the study if the bronchoscopy is terminated early due to patient safety concerns. Withdrawn if the subject withdraws consent for the study or the procedure. Subjects will retain the right to withdrawal consent at any time without consequences of any kind, including the right to future treatment.

There are no identified safety concerns, nor concerns of disease progression as this study will not interfere with diagnosis nor treatment. Individuals enrolled in the study will continue to receive treatment consistent with accepted standard of care. Based on study protocol diagnostic and outcome information will be obtained, but will not be used to alter medical decision making.

3.3.2. Follow-up for withdrawn subjects

Follow up by routine standard of care treatment. The intervention of this study is limited and has no lasting effects therefore long term follow up is not required.

Individuals that are withdrawn from the study will continue treatment and follow up visits consistent with standard of care. Currently there is no anticipated need to replace individuals withdrawn from the study as there will be concurrent active recruitment.

4. Recruitment Methods

4.1. Identification of subjects

Identified from pool of patients who will already be undergoing with planned flexible bronchoscopy and/or endobronchial ultrasound by an interventional pulmonologist in the operating room setting. They will be identified by review of the operating room schedule and through the interventional pulmonology clinic.

4.2. Recruitment process

Once potential subjects are identified from interventional pulmonology clinic or operating room schedule by the interventional pulmonology attending, patients will be evaluated and recommendations given prior to and independent of study enrollment. Individuals that meet inclusion criteria during in person questioning will be referred to a study team member. The team member will review the case and determine eligibility. If eligible, the team member will review the study with the subject, and obtain consent.

4.3. Recruitment materials

None.

4.4. Eligibility/screening of subjects

Not applicable.

5. Consent Process and Documentation

5.1. Consent Process

5.1.1.Obtaining Informed Consent

5.1.1.1.Timing and Location of Consent

For outpatients, consent for this study will be obtained on Penn State Hershey Medical center premises, at the interventional pulmonology clinic. Consent will be obtained immediately following a patient's medical office visit, by an authorized study team member. Consents will be obtained during normal clinic business hours. During clinic hours, translation services and impartial witnesses are available. Family members typically attend clinic visits and will be encouraged to participate in the consent process.

For inpatients, consent for this study will be obtained in their designated hospital room the day before their scheduled procedure. Consent will be obtained by an authorized study team member. Floor nurses as well as visiting family members will be available as impartial witnesses and will be encouraged to participate in the consent process.

For outpatients not previously seen in clinic, consent will be obtained in the pre-operative care unit the day of the scheduled procedure. Consent will be obtained by an authorized study team member. Family who are accompanying patient for procedure will be encouraged to participate in the consent process.

5.1.1.2.Coercion or Undue Influence during Consent

Consent will be obtained by the interventional pulmonologist who will be performing the procedure. Nursing staff is readily available in the clinic, medical floor and preoperative area for witness of consent. It will be explicitly stated that the care will not deviate from standard of care, and consent or abstention to this study will not affect the procedure they will receive, nor the level of medical care. If at any point the study subject expresses concern or unwillingness to proceed then the consent process will be terminated, not included in the study and explained that the same standard of care will be provided regardless.

The current IRB approved consent form will be used. Consent will be obtained following clinic visit in outpatient setting, after interventional pulmonology consult in inpatient setting and after procedure consent in pre-operative area, allowing detachment of the study and the medical care received. Patients are encouraged to have family members and other representatives present and will also be encouraged to stay for consent of the study. Questions will be encouraged, and answered adequately. Time will be given if the individual desires to discuss with family members or others. Voluntary enrollment will be explicitly stated. There are many Penn State employees that will be available as impartial witnesses in all three settings. Penn State translation services are available for non-English speaking individuals. If at any point the individual communicates they do not want to take part in the study, the consent process will immediately terminate.

5.1.2.Waiver or alteration of the informed consent requirement

Partial waiver will be obtained as per section 6.2 and 6.3.

5.2. Consent Documentation

5.2.1. Written Documentation of Consent

Written documentation of consent will be on the IRB approved consent form, and in an understandable language for the individual. The individual's name will be printed on page 1 of the form, and the person or representative will print, sign and date the consent form. The study team member obtaining consent will also print, sign and date, as well as the impartial witness. Finally a copy of the signed and dated consent will be given to the individual or representative and uploaded into the electronic medical record.

5.2.2. Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

Not applicable.

5.3. Consent – Other Considerations

5.3.1. Non-English Speaking Subjects

This study does not specifically target non-English speaking populations. If non-English speaking individuals are encountered, current IRB approved non-English short forms will be used for Spanish, Vietnamese, Russian, Italian, and French. The study team members obtaining consent will use English and translation performed to the desired language by the Penn State translation services.

5.3.2. Cognitively Impaired Adults

5.3.2.1. Capability of Providing Consent

Capacity will be determined at time of consent for procedure. If they do not have the capacity to consent for procedure, they will not be able to consent for the research study.

5.3.2.2. Adults Unable To Consent

Not applicable.

5.3.2.3. Assent of Adults Unable to Consent

Not applicable.

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

5.3.3.1. Parental Permission

Not applicable.

5.3.3.2. Assent of subjects who are not yet adults

Not applicable.

6. HIPAA Research Authorization and/or Waiver or Alteration of Authorization

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

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

Identifier will be retained through course of study as consent forms must be collected and stored.

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

Information must be obtained from the subject's electronic medical record during recruitment to determine eligibility and, in some cases, to confirm information discussed with the subject in regards to their medical history.

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

The waiver is requested only for recruitment to determine subject eligibility to ensure that no medical conditions that fall into the exclusion criteria are present and would thus preclude enrollment. This waiver will minimize the enrollment of subjects' who may ultimately fail to meet the study inclusion/exclusion criteria.

6.3. Waiver or alteration of authorization statements of agreement

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. Study Design and Procedures

7.1. Study Design

Patient is identified and consent is obtained in clinic, hospital room or pre-operative area. In the Same Day Pre-Anesthesia Care Unit they will receive Robitussin DM 20 ml syrup orally (Dextromethorphan 20mg) at least 60 minutes prior to bronchoscopy.

Once in the main procedure room patients will be induced into an anesthetic state using the following medications and dosing ranges. It will be titrated by anesthesiologist at bedside with goal to achieve hypnosis and apnea without profound bradycardia. The duration of the infusion is as required for the duration of the procedure.

- Propofol (1-3 mg/kg bolus and infusion of 50-200 mcg/kg), fentanyl 25-50 mcg on induction and alfentanil as a continuous infusion will be given at a rate of 0.5-2 mcg/kg/min with 1-3 mcg/kg bolus every 2-5min if need for further cough suppression. The Propofol infusion will be titrated to maintain BIS values between 40-60 for the duration of the procedure. When it is anticipated that the procedure will conclude within the next 10 minutes, the Propofol and alfentanil infusions will be stopped.

Contingency Plan: If despite the maximum dose of Propofol (150 mcg/kg/min) and alfentanil the patient continues to cough such that the procedure cannot be carried out, then Rocuronium will be administered IV (dose 20-40 mg at the discretion of the anesthesiologist) and its residual effect will be reversed using neostigmine (20-70 mcg/kg) and glycopyrrolate (10 mcg/kg) at the end of the procedure.

The patient's airway will be managed using a laryngeal mask airway (LMA) (Ambu Aura-I Size 4 or 5). Their airways will be anesthetized using a maximum of 2 mg per kg (max dose 160mg) of lidocaine, administered by one of the following techniques below. Randomization will be completed by selection of unmarked envelope.

1. "Spray as you go" - 16mL of 1% lidocaine sprayed in 4 mL aliquots. One at the vocal cords, one at midtrachea, one at left main stem bronchus and one at right mainstream bronchus.
2. Nebulizer – 2 % (preservative free) lidocaine (dose 2mg/kg max dose 160 mg) will be administered via a jet nebulizer, in the operating room over ten minutes, followed by procedure immediately after. The patient will be sitting propped up and his SpO2, EKG and BP will be monitored during this time. The jet nebulizer supply tube will be connected to central oxygen at 6 L/min and the duration of nebulization will be dryness of the nebulizing chamber or max of 10 minutes. [The Salter Series Small Volume Jet Nebulizer will be used.]
3. Vibrating Mesh Nebulizer – 2 % (preservative free) lidocaine (dose 2mg/kg max dose 160 mg) will be administered via a vibrating mesh nebulizer, in the operating room over ten minutes, followed by procedure immediately after. The patient will be sitting propped up and his SpO2, EKG and BP will be monitored during this time. The jet nebulizer will be

connected to central oxygen at 6 L/min and the duration of nebulization will be dryness of the nebulizing chamber or max of 10 minutes. [The Aerogen Solo Vibrating Mesh Nebulizer will be used.]

Patient will undergo scheduled procedure of flexible bronchoscopy or endobronchial ultrasound examination. During procedure, bronchoscopist and anesthesiologist will count the number of episodes of cough. Cough is defined as a cough which requires intervention such as additional dose of anesthetic or requires a pause in the procedure. During procedure, BIS monitor average, number of vasopressor interventions for MAP <60, induction time, procedure time and wake up time will be documented in the research record.

Following procedure, patient will be brought to post-op anesthesia care unit. Time to discharge readiness will be collected as well as the responses of the patient to the following questions:

- sore throat: absent, mild, moderate, severe
- cough: absent, mild, moderate, severe

7.2. Study Procedures

7.2.1. Visit 1

Study procedure is completed over the course of one day as described above in study design.

7.3. Duration of Participation

Duration is time from consent signing until patient is medically ready for discharge.

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

7.4.1. Description

160mg of 1% lidocaine is approved by the FDA for anesthetizing tracheobronchial tree. The mode of administration (spray as you go vs nebulized vs atomized) has been shown to have similar safety profile however efficacy has not been determined.

7.4.2. Treatment Regimen

Their airways will be anesthetized using 160mg of lidocaine, administered by one of the following techniques:

1. "Spray as you go" - 16mL of 1% lidocaine sprayed in 4 mL aliquots. One at the vocal cords, one at midtrachea, one at left main stem bronchus and one at right mainstream bronchus.
2. Jet Nebulizer – 8 mL of 2 % lidocaine administered via a jet nebulizer over ten minutes, followed by procedure immediately after.
3. Vibrating Mesh Nebulizer – 8 mL of 2 % lidocaine administered via a vibrating mesh nebulizer over ten minutes, followed by procedure immediately after.

7.4.3. Method for Assigning Subject to Treatment Groups

Subject forms will have administration mode documented and will be placed in sealed envelopes. Immediately prior to procedure, envelope will be opened to determine which mode of lidocaine administration will be performed. Lauren Ventola will secure all envelopes within locked cabinet in Jennifer Toth's office. Subject will be told of their assigned treatment group. Inpatient/Outpatient will be a 50/50% stratification.

7.4.4. Subject Compliance Monitoring

Not required to be monitored as medication is administered by the anesthesiologist or bronchoscopist prior to or during the procedure

7.4.5. Blinding of the Test Article

Mode of administration will not be blinded to anesthesiologist or bronchoscopist.

7.4.6. Receiving, Storage, Dispensing and Return

7.4.6.1. Receipt of Test Article

Lidocaine will be ordered from the pharmacy. The vibrating mesh nebulizer and jet nebulizer will be set up by anesthesiologist and spray as you go will be set up by OR staff and bronchoscopist.

7.4.6.2. Storage

Same medication obtained from pharmacy is used across all three groups, the mode of administration is only part changed and will be completed by anesthesiologist and/or bronchoscopist.

7.4.6.3. Preparation and Dispensing

Mode of administration will be determined day of procedure by selection of randomized, sealed envelopes containing subject form with administration mode. The atomized and nebulized lidocaine will be prepared and administered by the anesthesiologist. The "spray as you go" lidocaine will be prepared by the scrub nurse and administered by the bronchoscopist. Preparation involves loading medication into administration devices.

Medication will not be dispensed directly to subject.

7.4.6.4. Return or Destruction of the Test Article

Not applicable.

7.4.6.5. Prior and Concomitant Therapy

Dextromethorphan syrup 90mg will be given 60 minutes prior to procedure. Post-procedure, subject will be able to use nebulized albuterol. No medications are contraindicated.

8. Subject Numbers and Statistical Plan

8.1. Number of Subjects

48 patients randomly assigned to lidocaine application technique (24 in topical, 12 in jet nebulizer and 12 in vibrating mesh nebulizer). Among each group there will be stratification of flexible bronchoscopy/endobronchial ultrasound procedures and inpatient/outpatient.

8.2. Sample size determination

Not applicable.

8.3. Statistical methods

Descriptive statistics will be used for continuous variables, and presented as medians and interquartile ranges. Categorical variables will be expressed as percentages. The estimated sample size within our institution is 48 patients.

9. Confidentiality, Privacy and Data Management

See Research Data Plan Review Form.

10. Data and Safety Monitoring Plan

10.1. Periodic evaluation of data

Data will be evaluated half way through and at completion of study by primary investigator

10.2. Data that are reviewed

Data collected on subject forms with comparison to Red Cap data.

10.3. Method of collection of safety information

Safety data will be collected at the time of the procedure by the primary investigator.

10.4. Frequency of data collection

With each procedure and data collection.

10.5. Individuals reviewing the data

The primary investigator as well as study team members.

10.6. Frequency of review of cumulative data

Half way through bronchoscopy data collection and at completion. Safety data will be collected during each procedure.

10.7. Statistical tests

Descriptive statistics will be used for continuous variables, and presented as medians and interquartile ranges. Categorical variables will be expressed as percentages.

10.8. Suspension of research

Will be based on safety data collection following each subject's bronchoscopy.

11. Risks

There is the potential risk of loss of confidentiality with this study due to consent being required however no personal identifiers will be attached to the data we collect. There is no other foreseeable risk to the patients involved in this study. All medications and procedures fall within standard treatment and standard of care. The only variable will be the delivery method of the medication used during bronchoscopy. There is no risk to the researchers or hospital staff either. Loss of confidentiality is always a potential risk, but no protected health information will be maintained or collected, minimizing this risk. Risk of randomization is also present however all modalities are considered standard of care.

12. Potential Benefits to Subjects and Others

12.1. Potential Benefits to Subjects

No direct benefit to subjects.

12.2. Potential Benefits to Others

Benefit to society by determining what mode of application of lidocaine prevents severe cough and improves efficiency and decreases potential risks during flexible bronchoscopy and endobronchial ultrasound.

13. Sharing Results with Subjects

Not applicable.

14. Subject Stipend (Compensation) and/or Travel Reimbursements

Not applicable.

15. Economic Burden to Subjects

15.1. Costs

Not applicable.

15.2. Compensation for research-related injury

Not applicable.

16. Resources Available

16.1. Facilities and locations

Pre-anesthesia care unit, floor room or interventional pulmonology clinic where consent process will take place.

Pre-anesthesia care unit where patient will receive dextromethorphan.

Main Procedure Room 1 where lidocaine will be administered and procedure completed. Will collect number of severe coughs, amount of anesthesia, time of procedure and wake up time.

Post-anesthesia care unit where time to discharge readiness, patient cough severity and sore throat severity will be collected.

16.2. Feasibility of recruiting the required number of subjects

There are over 600 combined flexible bronchoscopies performed per year, and include a combination of basic bronchoscopy and EBUS.

16.3. PI Time devoted to conducting the research

The PI will be responsible for oversight of recruitment, oversight of data entry accuracy, and primary data analysis. The PI will also have initial overview to ensure subject safety.

16.4. Availability of medical or psychological resources

Not applicable.

16.5. Process for informing Study Team

The research team currently consists of the principal investigator and four co-investigators. If additional members are added, they will be educated on the confidentiality and data management principles outlined in section 9.

17. Other Approvals

17.1. Other Approvals from External Entities

Not applicable.

17.2. Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the “Supporting Documents” page in CATS IRB. This form is available in the CATS IRB Library.

☐ 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 in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the “Supporting Documents” page in CATS IRB. This form is available in the CATS IRB Library.

☐ Clinical Research Center (CRC) Advisory Committee– All campuses – 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 – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the “Supporting Documents” page in CATS IRB. This form is available in the CATS IRB Library.

☒ 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 – Hershey 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 Hershey Cancer Institute Scientific Review Committee 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 at: <http://www.pennstatehershey.org/web/irb/home/resources/investigator>

18. Multi-Site Research

18.1. Communication Plans

Not applicable.

18.2. Data Submission and Security Plan

Not applicable.

18.3. Subject Enrollment

Not applicable.

18.4. Reporting of Adverse Events and New Information

Not applicable.

18.5. Audit and Monitoring Plans

Not applicable.

19. Adverse Event Reporting

19.1. 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”. <ul style="list-style-type: none"> • <i>Reasonable possibility.</i> 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.

19.2. Recording of Adverse Events

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.

19.3. Causality and Severity Assessments

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.

19.4. Reporting of Adverse Reactions and Unanticipated Problems to the FDA

19.4.1. Written IND/IDE Safety Reports

Not applicable as new drug is not being studied, only comparison of mode of application.

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

Not applicable as new drug is not being studied, only comparison of mode of application

19.5. Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

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.

19.6. Unblinding Procedures

Modes of administration are not blinded.

19.7. Stopping Rules

Not applicable.

20. Study Monitoring, Auditing and Inspecting

20.1. Study Monitoring Plan

20.1.1. Quality Assurance and Quality Control

The principal investigator will be monitoring the conduct of the study throughout, data will be reviewed at 50% recruitment and 100% recruitment.

20.1.2. Safety Monitoring

Adverse events will be identified and recorded on each subject form by the monitor and will be reviewed by the primary investigator who is present during all procedures.

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 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.

21. Future Undetermined Research: Data and Specimen Banking

21.1. Data and/or specimens being stored

Not Applicable. No specimens will be collected, and data will not be stored once this study is completed.

21.2. Location of storage

Not applicable

21.3. Duration of storage

Not applicable

21.4. Access to data and/or specimens

Not applicable

21.5. Procedures to release data or specimens

Not applicable

21.6. Process for returning results

Not applicable

22. References

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D Stolz, P C Haged et al. Nebulized Lidocaine for Flexible Bronchoscopy. Chest 2005; 128; 1756-1760.

M Wahidi, et al. American College of Chest Physicians Consensus Statement on the Use of Topical Anesthesia, Analgesia and Sedation during Flexible Bronchoscopy in Adult patients. Chest 2011; 140 (5): 1342 – 1350

M Dreher, C Cornelissen, et al. Nebulized versus Standard Local Application of Lidocaine during Flexible Bronchoscopy: A Randomized Controlled Trial