Official title: Auris Robotic Endoscopy System (ARES) for Bronchoscopy

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Document date: 5 October 2017

TITLE PAGE

Auris Robotic Endoscopy System (ARES) for Bronchoscopy – NSR Study

STUDY TITLE: Auris Robotic Endoscopy System (ARES) for Bronchoscopy – NSR Study

A SINGLE-CENTER, PROSPECTIVE, SINGLE ARM STUDY TO EVALUATE THE PERFORMANCE OF THE AURIS ROBOTIC ENDOSCOPY SYSTEM (ARES) FOR BRONCHOSCOPIC PROCEDURES

PROTOCOL: PRT DD082015

VERSION: 9

DATE: October 5, 2017

Revision History

Version	Description of Change
3	Released for IRB Submission (provided to ECH Coordinator)
4	Revised list of Risks to match ICF (Page 13-14 Section 1.2.1)
5	Clarified bronchoscopic risk (Page 14 Section 1.2.1)
6	Resolve protocol inconsistencies and make revisions to match ICF
7	Revised protocol to reflect anticipated product development and to clarify study endpoints
8	Included the final device description and clarified study endpoints
9	Resolve inconsistency with primary and secondary endpoint

Clinical Investigation Plan (CIP) and Protocol
Identification of Responsibility Page

Auris Robotic Endoscopy System (ARES) for Bronchoscopy – NSR Study

A SINGLE-CENTER, PROSPECTIVE, SINGLE ARM STUDY TO EVALUATE THE PERFORMANCE OF THE AURIS ROBOTIC ENDOSCOPY SYSTEM (ARES) FOR BRONCHOSCOPIC PROCEDURES

(PTL DD082015)

The Study will be performed in accordance with the relevant parts of Title 21 CFR Parts 812, 50, 54, 56 and ISO 14155-1 / 14155-2.1; the ICH Guidelines for Good Clinical Practices (E6), the Declaration of Helsinki, and any regional and/or national regulations

Sponsor:	Auris Surgical Robotics, Inc [redacted]	
Principal Investigators / [redacted]	[redacted]	
Date of Issue:	October 5, 2017 Version 9	

This protocol contains confidential information for use by the Investigators and their designated representatives participating in this clinical investigation. It should be held confidential and maintained in a secure location.

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Auris Robotic Endoscopy System (ARES) for Bronchoscopy – NSR Study

Approval Page

STUDY TITLE:	Auris Robotic Endoscopy System (ARES) for Bronchoscopy – NSR Study **A SINGLE-CENTER, PROSPECTIVE, SINGLE ARM STUDY TO EVALUATE THE PERFORMANCE OF THE AURIS ROBOTIC ENDOSCOPY SYSTEM (ARES) FOR BRONCHOSCOPIC PROCEDURES**
PROTOCOL NUMBER:	PRT DD082015
VERSION NUMBER:	9
DATE:	October 5, 2017

We, the undersigned, have read and approve the protocol specified above and agree on its content.

[redacted]

ARES study – Investigator's Signature Page

STUDY TITLE: Auris Robotic Endoscopy System (ARES) for Bronchoscopy – NSR Study

A SINGLE-CENTER, PROSPECTIVE, SINGLE ARM STUDY TO EVALUATE THE PERFORMANCE OF THE AURIS ROBOTIC ENDOSCOPY SYSTEM (ARES) FOR BRONCHOSCOPIC PROCEDURES

STUDY CENTER: [redacted]

I, the undersigned, have read and understand the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol. In addition, when applicable, I agree to enlist sub-investigators who also agree to perform and conduct the study as described in the protocol.

[redacted]

DATE

Protocol Synopsis

Auris Robotic Endoscopy System (ARES) for Bronchoscopy – NSR Study

A SINGLE-CENTER, PROSPECTIVE, SINGLE ARM STUDY TO EVALUATE THE PERFORMANCE OF THE AURIS ROBOTIC ENDOSCOPY SYSTEM (ARES) FOR BRONCHOSCOPIC PROCEDURES

Primary Objective	The objective of this study is to evaluate the performance of the novel Auris Robotic Endoscopy System (ARES) during bronchoscopy procedures. Product features may be added and/or revised during the conduct of the study and will be evaluated by the physician. Appropriate notifications to Institutional Review Board (IRB) will be made of any revisions. The study is a Non-Significant Risk (NSR) feasibility study with no specific statistical study size or power.
Test Device	Monarch Robotic Endoscopy Platform, the next generation of Auris Robotic Endoscopy System (ARES)
Control Device	None
Indication for Use **510K #:** K152319	The previous ARES is FDA cleared medical device (**510K #:** K152319) intended to provide bronchoscopic visualization of patient airways. The Auris Robotic Endoscopy System (ARES) is intended to be used by qualified physicians to provide visualization to the bronchial tree during bronchoscopic procedures. The Monarch Robotic Endoscopy Platform (Monarch Platform) and its accessories are intended to provide bronchoscopic visualization of and access to patient airways for diagnostic and therapeutic procedures.
Hypotheses	No formal statistical hypotheses are defined. It is believed that the Auris system will be capable of enhancing access to peripheral lung lesions.
Study Design	A single-center, prospective, single arm study to evaluate the performance related to the use of the ARES during bronchoscopic procedures. The Auris system will be used in conjunction with a navigational bronchoscopy procedure.
Number of Patients	The study will enroll up to 60 patients. It is expected that enrollment will take up to 6 months.

Sites	[redacted]
Duration of Study	Each enrolled subject will be followed up to 6 weeks (± 7 days) post procedure.
Primary Effectiveness Endpoint	The primary effectiveness endpoint is the completion of the intended bronchoscopic procedure with the ARES, as defined by the ability to acquire tissue with biopsy tools.
Secondary Effectiveness Endpoints	The following will be considered secondary endpoints: • Identification of correct bronchi leading to the targeted lesions • Ability to localize targeted lesion • Alignment capabilities • Time to REBUS confirmation (lesion localization), time to the tissue acquisition confirmation, Total procedure time (from introduction to removal of the bronchoscope) and procedure interruptions • Diagnostic yield • Conversion to conventional bronchoscopic procedure • Anesthesia time
Primary Safety Endpoint	Device or procedure related adverse events (AEs).
Secondary Safety Endpoint	Complications unrelated to device.
Follow-Up Schedule	Each enrolled subject will be followed up to 6 weeks ±7 days post procedure.

Pre-Operative Inclusion Criteria	1. 18 to 80 years of age; 2. Capable and willing to give informed consent; 3. Acceptable candidate for an elective, non-emergent bronchoscopic procedure; 4. Solid peripheral lung lesions suspected of malignancy, between 1.5-7cm in size identified on thin slice CT scan with 30 days of the intended bronchoscopy
Pre-Operative Exclusion Criteria	Subjects will be excluded from participating in this Study if they meet any of the following criteria prior to initiation of the endoscopic procedure: 1. Medical contraindication to bronchoscopy; 2. Ground glass opacity lesions on pre-procedure CT 3. Participation in any other clinical trial 30 days before and throughout the duration of the study; 4. Uncontrolled or irreversible coagulopathy; 5. Female subjects who are pregnant or nursing or those of child-bearing potential refusing a pregnancy test; 6. CT scan done over a month before the bronchoscopy procedure.
Intra-Procedure Exclusion Criteria	Any presenting condition discovered intra-procedurally that in the opinion of the investigator would make participating in this study not in the patient's best interest.

Study Sponsorship	
Sponsor	[redacted]

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1. Introduction

Lung cancer is the leading cause of cancer deaths in the United States, having a higher mortality than prostate, colon, and breast cancers combined. Approximately 220,000 patients are newly diagnosed with lung cancer each year and over 155,000 patients die from the disease annually in the United States.[1]

Recently, the National Lung Screening Trial found that 24% of high-risk patients who underwent low-dose computed tomography (CT) scans had lesions suspicious for lung cancer.[2]

As the technology to identify lesions improves and screening for lung cancer in at-risk individuals advances, there will be increased requirements for minimally invasive tissue diagnosis of these lesions.

The early and accurate diagnosis of lung cancer is critical. However, many peripheral lung lesions are beyond the reach of conventional bronchoscopes. Additionally, alternative techniques, such as CT-guided or surgical biopsy, can carry increased risks to the patient. Diagnostic yield of flexible bronchoscopy is limited by its inability to guide biopsy instruments directly to the lesion. Varying technologies have been proposed to guide endobronchial biopsies, such as electromagnetic navigation, endobronchial ultrasound (EBUS) and computed tomography fluoroscopy.[3] However, the correlation of real-time guidance and the ability to precisely direct a biopsy instrument is critical to biopsy success.

Over the past two decades there has been extensive development of “robotic” medical device systems that result in “intuitive” or instinctive control of medical devices providing enhanced stability and control. The term “robotic”, in this case, refers not to autonomous movement but rather electromechanical, software driven control by the physician operator. Typically, these “robotic” systems remain under continuous and direct control by the physician operator. Good examples of these robotic devices include Intuitive Surgical’s “da Vinci” surgical control system and Hansen Medical’s catheter control system.

All of these control systems, both surgical and interventional, are classified by the United States Food and Drug Administration (FDA) as Class II devices with at most moderate risk and are subject to the “Pre-Market Notification” or “510(k)” clearance process. FDA has historically determined these devices to be similar enough to their conventional manual device counterparts that a “substantial equivalence” determination can be made. Thus, these devices have historically been excluded from the more rigorous “Pre-Market Approval” or PMA process used for Class III devices found by FDA to carry higher risk.

The Auris Robotic Endoscopic System (ARES) is a “robotic” or electromechanical, software driven endoscopy system designed to be used by qualified physicians to provide visualization to the bronchial tree during bronchoscopic procedures and, therefore, to guide a bronchoscope and associated tools to predetermined points within the bronchial tree. FDA has cleared the previous

[1] Jemal A, Siegel R, Xu J, Ward E. Cancer Statistics 2010. Ca Cancer, J Clin 2010;60:277–300.

[2] Aberle R, Adams AM, Berg CD, et al. National lung screening trial research team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395–409.

[3] Gilbert C, Akulian J, Ortiz R, Lee H, Yarmus L. Novel bronchoscopic strategies for the diagnosis of peripheral lung lesions: present techniques and future directions. Respirology. 2014 Jul;19(5):636-44.

ARES, like the Intuitive Surgical and Hansen Medical devices, as a Class II device under the 510(k)-clearance process (510K #: K152319). Further, FDA has classified endoscopes in general as being "non-significant risk" or NSR devices (see below).

The ARES has been extensively tested in porcine and cadaver studies. The system has been also tested in a clinical pilot studies in humans to remove urinary stones and in a separate study to obtain lung biopsy specimens. Herein, we propose a clinical trial with this enhanced bronchoscopic system to provide visualization to the bronchial tree during bronchoscopic procedures and, therefore, to guide a bronchoscope and associated tools to obtain diagnostic tissue from bronchopulmonary lesions suspicious of malignancy.

1.1. Non-Significant Risk (NSR) Rationale

FDA defines a "Significant risk device" as an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (2) is for use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject; (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to a subject. Examples of Significant risk devices include sutures, cardiac pacemakers, hydrocephalus shunts, and orthopedic implants (see copy of FDA guidance attached). Studies of devices that pose a significant risk require both FDA and an Institutional Review Board (IRB) approval prior to initiation of a clinical study. FDA approval is obtained by submitting an IDE application to FDA (§812.20).

Non-significant risk (NSR) devices are devices that do not pose a significant risk to the human subjects. An NSR device study requires only IRB approval prior to initiation of a clinical study. Sponsors of studies involving NSR devices are not required to submit an IDE application to FDA for approval. In the attached guidance document, FDA lists several specific endoscopes as examples of NSR devices. The listed endoscopes include:

- Conventional Gastroenterology and Urology Endoscopes and/or Accessories
- Conventional Laparoscopes, Culdoscopes, and Hysteroscopes

Based upon these examples and the NSR definition, Auris Surgical Robotics believes that the ARES when used in the referenced study clearly falls into the NSR category.

In addition, we consider this clinical study and the system under investigation to fall into the category of non-significant risk for patients whom meet the selection criteria for several reasons:

- The ARES is not implanted. The system is only used to guide and steer an endoscope. Instruments inserted through the working channel of the endoscope during endoscopic procedures are not included in this study and will be conventional endoscopic tools used in standard-of-care procedures to perform specific tasks such as biopsy. Because of its small, flexible, atraumatic design, the Auris bronchoscope clearly does not present a potential for serious risk to the health, safety, or welfare of a subject. The biopsy alternative method called transthoracic needle aspiration (TTNA) to obtain lung tissue biopsies is the use of a long needle to penetrate through the chest wall into the lung to access the target lesion.

Transthoracic needle aspiration has a substantial 25% pneumothorax rate and 5% pneumothorax rate requiring a chest tube. The bronchoscopic technique does not penetrate the chest wall and therefore significantly decreases the co-morbidity profile.

- The ARES is not used in supporting or sustaining human life and therefore, again does not represent a potential for serious risk to the health, safety, or welfare of a subject.
- The ARES is not of substantial importance in diagnosing, curing, mitigating, or treating disease during these studies because standard-of-care tools will be used to perform any diagnostic or therapeutic procedures. Specifically, conventional endoscopic tools are used to perform any diagnostic or therapeutic treatments, e.g., obtain biopsy specimens. At no time is the ARES used to guide patient treatment.
- The protocol was developed in concert with the study's investigator who is well-known in the area of interventional pulmonology. In addition, [redacted] has had multiple training sessions with the ARES and will have additional time and instruction with the system. The site, El Camino Hospital, was chosen because of the proven track record and expertise in the field of interventional pulmonology.
- The environment or room to be used for this proposed procedure will provide careful usage (non-chaotic as oppose to an emergency room) of the system with the additional option to revert to a standard manual bronchoscope if any issues develop during the procedure with the ARES. This environment will include proper personnel in the room including the investigators and bronchoscopy nurses. Company representatives will also be present for each procedure, in order to provide optimal support for each case using the ARES.
- The Auris development team involved with this system has the breadth and experience on working on medical devices. The ARES was both designed by an experienced team of individuals that have over 10 decades of cumulative experience bringing both medical and robotic devices to the market. The ARES was developed in compliance with guidelines outlined in ISO 13485, including but not limited to Risk Analysis, Design Control and both Design Verification and Validation Activities. As such, the ARES has been validated to work as designed for the clinical investigation.
- ARES was evaluated in a human pilot study that focused on guidance of standard of care tools for the biopsy of suspicious lesions. This study was completed in October of 2014 and biopsied 15 patients. No cases of pneumothorax were reported from the study. There were three adverse events reported in the study. All three adverse events were non-serious with unrelated causality to the system use.

In the light of these facts, it is the opinion of Auris Surgical Robotics that the system used within the criteria of this study protocol is a non-significant risk to the patients whom meet the selection criteria.

1.2. Specific Risk and Benefits

1.2.1. Risks

With any bronchoscopic procedure, there is the possibility of the following risks listed in the

order of estimated frequency.[1] Below risks are related only to bronchoscopy procedure and not for biopsy:

- Common: Between 1 and 5%
  - Shortness of breath
  - Coughing
  - Wheezing
- Rare: Between 0.1 and 1%
  - Bleeding/Hemoptysis
  - Lung Leak or Collapse
  - Infection/Pneumonia
  - Transitory Fever
- Extremely Rare: Less than 0.1%
  - Bronchoscopic Airway Puncture
  - Cardiovascular Event/Irregular heartbeat
  - Bronchial Asthma
  - Respiratory Failure
  - Death

In the event that any of these were to occur, the study subject will be treated for the condition. Some subjects may experience wheezing, coughing, or shortness of breath during the first few days following a bronchoscopy procedure.

Anesthesia Risk

There is a potential risk of developing side effects associated with the use of anesthesia. The risks of anesthesia depend on the agents and/or gases used. The risks of anesthesia include postoperative pain, nausea and vomiting, dizziness, drowsiness, shivering, liver toxicity and/or cardiovascular events. Trained professionals with extensive experience and expertise who routinely administer local anesthesia with conscious sedation to patients requiring multiple procedures will be responsible for the induction and associate monitoring required for this study. In addition, study patients will undergo extensive monitoring throughout the recovery period.

Risk Mitigation

Risks during study participation will be minimized by the following:

The study protocol was developed with an investigator that is well-known in the area of interventional pulmonology. The site was chosen because of proven expertise in the field of interventional pulmonology. All Investigators performing the procedure using the ARES System under the clinical protocol will undergo a Training Program, which includes elements of both a didactic and training program. Proficiency must be demonstrated prior to use in humans. [redacted] has had several days of training time with the system

[1] *FUMIHIRO ASANO, et al., Deaths and complications associated with respiratory endoscopy: A survey by the Japan Society for Respiratory Endoscopy in 2010 Respirology (2012*) **17**, 478–485

and has demonstrated proficiency with the system. Pre-clinical, *in vitro* and *in vivo* testing has been performed in order to optimize the device safety and function.

1.2.2. Benefits

The primary potential benefit of participation is the occurrence of a successful biopsy of tissue for pathological evaluation which is necessary to support specific treatment. Results will be evaluated in this study and will further support the development of bronchoscopic equipment for pulmonary and thoracic physicians.

2. Study Device Description

Monarch Robotic Endoscopy Platform, the next generation of Auris Robotic Endoscopy System (ARES), consists of three major components, the Auris Robotic Cart (ARC), the Tower and the Robotic Endoscope. The current system is the next iteration of the Auris Robotic Endoscopy System (ARES) that originally received 510(k) clearance as a Class II device in May 2016. The system has several components that interface to the Auris Robotic Cart including: The Fluidics Control, Electro-Magnetic Field generator, and Reference Electro-Magnetic sensors.

2.1. Auris Robotic Cart

The Auris Robotic Cart (ARC) is a carrier for the robot arms. It includes two robotic arms which contain rotary pulleys to actuate the drive cables in the bronchoscope. The Cart houses the electronic systems required to power and operate the robotic system. Automated lift controls will raise and lower the height of the robotic arms. The cart handle allows the cart to be maneuvered so that the cart wheels can be directionally locked. An embedded touch-screen on the cart handle provides feedback during system setup.

An Emergency Stop button (Estop) sits on the Auris Robotic Cart and is positioned such that a clinical assistant has easy access to it.

The following image shows the Auris Cart with the robotic arms in the stow position (right) and load bronchoscope position (left):

Figure 1. Auris Robotic Cart

2.2. Auris Tower

The Auris Tower houses two computers that run the system, a Non-Real Time Computer and a Real-Time Computer. The Non-Real Time computer takes the inputs from the pendant, keyboard, mouse, camera, EM Localization/Targeting System and Power Distribution Unit.

The Non-Real Time computer also contains an interface to the micro camera at the tip of the Endoscope. The camera interface performs the necessary image processing and generates output video streams.

The robotic system algorithms are also implemented on the Real-Time computer. The Real-Time computer receives inputs from the Non-Real Time computer. The network handles communication between the two computers, robotic arms and Power Distribution Unit.

The tower provides connectivity for the bronchoscope camera and lighting, as well as the fluidics system.

A single monitor is integrated into the Tower to display real time video captured from the bronchoscope camera overlaid with information on the status of the robotic system. Lastly, an E-stop sits on the Auris Tower and is positioned such that a clinician has easy access to it.

The following image show the Tower:

Figure 2. Auris Tower

The Tower includes an endoscopy controller that allows the clinician to control the system during a procedure. On the controller, two joysticks are used to drive and articulate the bronchoscope while various buttons are used to control irrigation, aspiration and the device state. The following image shows the endoscopic controller:

Figure 3. Auris Endoscopy Controller

2.3. *Bronchoscope*

The Auris Bronchoscope is a comprised of two collinear and concentric devices, the inner scope and the outer sheath both of which possess 4-way steering control. This configuration enables the capability of telescoping, which enhances the bronchoscope stability and access capability.

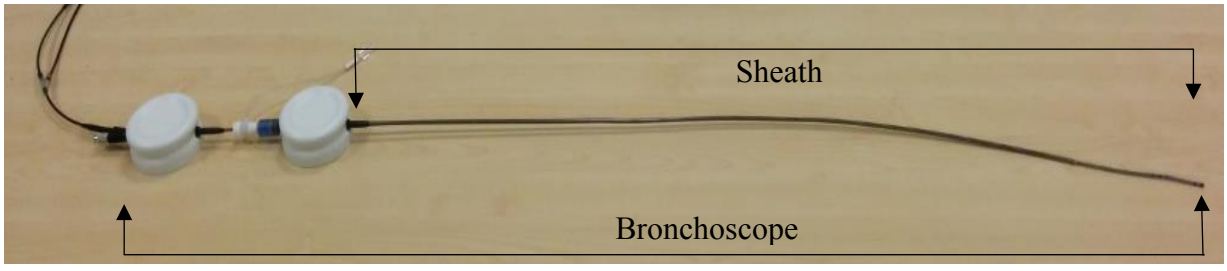

Figure 4. Auris Robotic Endoscope

The bronchoscope includes a camera that provides the operative perspective, an integrated light source in the scope handle and a 2.1 mm inner diameter working channel for the passing of tools.

The scope and sheath has a distal section capable of achieving articulation in pitch, yaw and any combination of the two to enable precise control while driving the bronchoscope. Proximally, the scope is equipped with a valve to facilitate the insertion and sealing of various ancillary devices, such as a biopsy needle. Additionally, the proximal section routes irrigation and aspiration to the shared working channel.

2.4. Auris Robotic Cart External Components

The system has several components that interface to the Auris Robotic Cart including: Fluidics Control, Electro-Magnetic Field generator, and Reference Electro-Magnetic sensors.

Fluidics Control

The fluidics control consists of a peristaltic pump and controlled valves. The fluidics control can dispense a fluid through a single-use tubing set into the endoscope. The fluidics control actuates aspiration of fluids to an external vacuum source.

Electro-Magnetic Field generator

The Electro-Magnetic Field generator is used as part of the system for navigation guidance.

Reference Electro-Magnetic sensors

The Reference Electro-Magnetic sensors are used to monitor the patient position relative to the Electro-Magnetic Field Generator.

Device Labeling

A copy of the Instructions for Use (IFU) will be included with the devices.

3. Prior Investigation

The ARES System, has undergone careful and comprehensive *in-vivo* and *ex-vivo* pre-clinical studies. The system was developed under 21 CFR 820 design control compliant design control process. The safety and performance of the ARES system was also successfully used in humans for ureteroscopic applications in 16 human patients and for bronchoscopic applications in 15 human patients.

Summaries of previous investigations are presented below.

3.1. ARES Biocompatibility Study

Title: Testing for Externally Communicating Devices

Completed: (Available Upon Request)

Objective: To evaluate the biocompatibility of the appropriate components of the ARES

Methods: The tests that were performed are listed in the table below.

Biocompatibility Tests for External Communicating Devices	
Cytotoxicity: MEM Elution	Completed, Passes
Sensitization: Local Lymph Node Assay	Completed, Passes
Irritation: Intracutaneous Reactivity	Completed, Passes

Conclusions: All of these tests will be concluded prior to the start of the robotic procedures. The study investigators will be updated on the outcome or justifications of these evaluations.

3.2. Bronchoscopy In-vivo Pre-Clinical Study

Title: Acute Evaluation of the Auris Robotic Endoscopic System (ARES) for Bronchoscopy
Start/Complete dates: 2/20/2014 to 5/01/2014
Objectives:

- To acutely evaluate the following in bronchi in vivo in porcine models:
  - The safety profile of the procedure
    - Document any adverse events or findings
  - The performance of the Auris system
    - Navigation
      - Visual
      - Movement
  - Biopsy

- To evaluate the ability for an operator/physician to consistently/accurately control and navigate in an animal bronchial tree

Results:

- Number of animals
  - 10
- Biopsy evaluation
  - Successful use of both biopsy forceps and needle aspiration devices
- Navigation
  - Successful robotic navigation throughout the bronchial tree
- Safety
  - One pneumothorax
    - The physician user was navigating without vision and testing peripheral reach of the ARES system.
  - Emergency removal successful

Conclusion

- Operators/physicians can be trained to successfully navigate throughout the bronchial tree with the ARES system.
- The ARES system appears to be safe with proper usage including navigation with vision
- The ARES system appears to provide a means for successful tissue biopsy using forceps and needle aspiration devices

3.3. Ureteroscopy Clinical Pilot Study

Title: Robotic Endoscopy Pilot Study for the treatment of Renal Calculi
Start/Complete dates: 6 to 10 June 2014
Objectives/Study Design:

- The primary objective of this study is to evaluate the safety and performance of the ARES for the treatment of renal and/or ureteral calculi.
  - This is an unblinded, single-arm, single site study.
  - The study was approved by the ethics committee at the Muljibhai Patel Urological Hospital.

Results

- 16 patients
  - 24 stones removed
- Safety
  - No surgical or post-operative complications

Conclusions

- Operators/physicians can be trained to successfully navigate throughout the bronchial tree with the ARES system.

- The ARES system appears to be safe with proper usage including navigation with vision
- There were no unanticipated adverse events from the procedure

3.4. Bronchoscopy Clinical Pilot Study

Title: Performance and safety evaluation of a robotic bronchoscopy system for diagnosis of suspected lung cancer: A Clinical Pilot Study
Start/Complete dates: 13 September 2014 to 5 October 2014
Objectives:

- The primary objective of this study is to evaluate the safety and performance of the ARES for the access of suspicious lung cancer lesions
- This is an unblinded, single-arm, single site study
- The study was approved by the ethics committee at the Hospital Clínica Bíblica and WIRB (Western Institutional Review Board)

Results

- 15 patients
  - Enrolled/completed the study
  - Able to navigate and biopsy from 15 of the 15 (100%) study procedures
- Safety
  - No surgical or post-operative complications

Conclusions

- Operators/physicians can be trained to successfully navigate throughout the bronchial tree with the ARES system.
- There were no unanticipated adverse events from the procedure

4. Study Objective

The objective of this study is to evaluate the performance of the Monarch Robotic Endoscopy Platform, the next generation of Auris Robotic Endoscopy System (ARES) during bronchoscopy procedures. Information obtained during this feasibility study may be used to guide future product development.

Product features may be added and/or revised during the conduct of the study and will be evaluated by the physician. The IRB will be kept informed of any product revisions as appropriate.

The study is a NSR feasibility study with no specific statistical study size or power.

5. Study Design

5.1. Overview

A single-center, prospective, single arm study to evaluate the performance of the ARES System during bronchoscopy procedures. The Auris system will be used in conjunction with a navigational bronchoscopy procedure.

5.2. Sample Size

The study will enroll up to 60 patients.

It is expected that enrollment will take up to 6 months.

5.3. Investigational Site

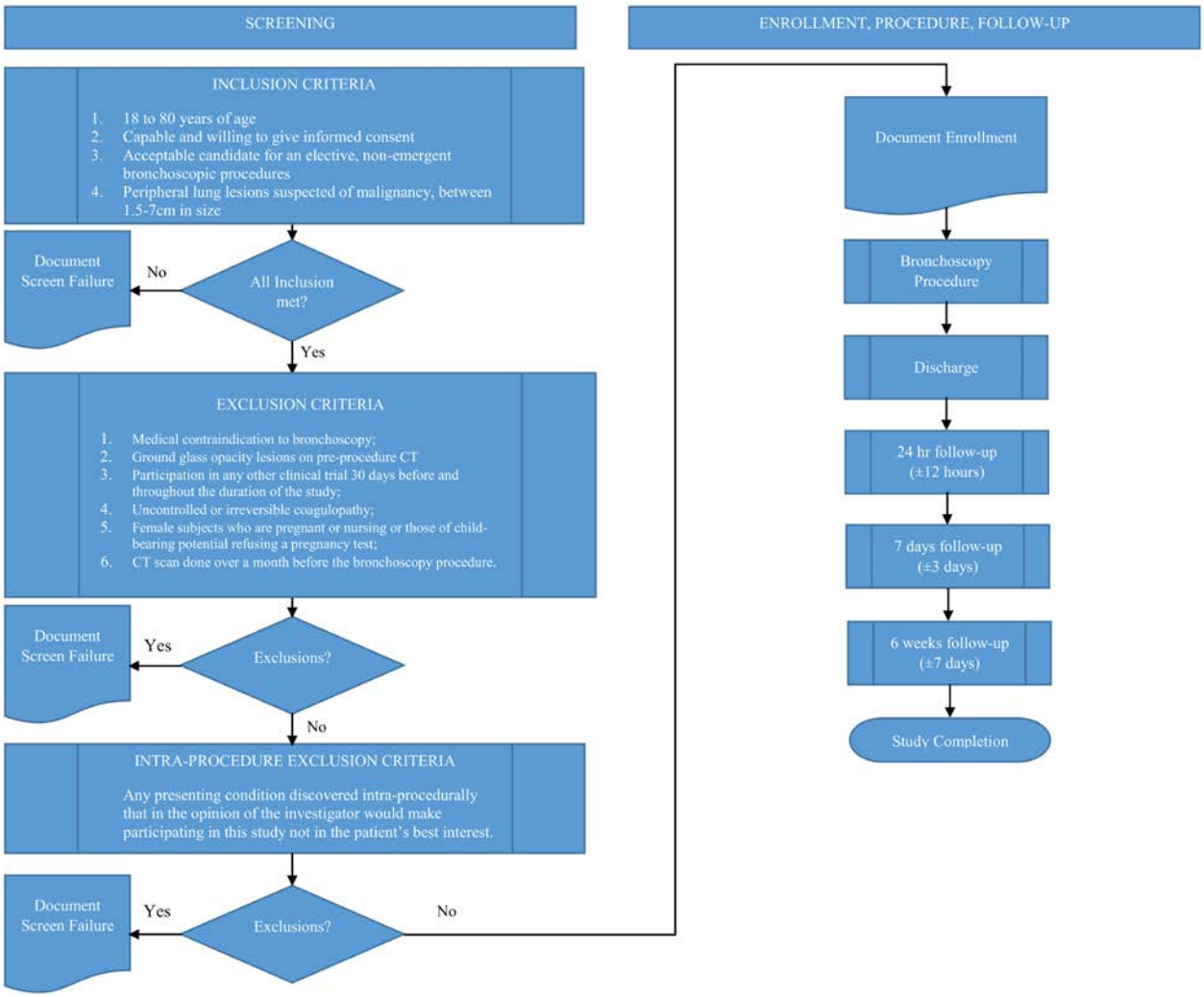

Figure 5. Schematic of Study Design

6. Study Population

6.1. Selection Criteria

The following pages outline the specific inclusion and exclusion criteria for the study. Before study enrollment, a patient must meet all of the inclusion and none of the exclusion criteria.

6.1.1. Pre-Procedure Inclusion Criteria

All subjects are required to meet the following inclusion criteria in order to be considered eligible for participation in this Study:

Pre-Operative Inclusion Criteria	1. 18 to 80 years of age; 2. Capable and willing to give informed consent; 3. Acceptable candidate for an elective, non-emergent Bronchoscopic procedure; 4. Solid peripheral lung lesions suspected of malignancy, between 1.5-7cm in size identified on thin slice CT scan with 30 days of the intended bronchoscopy

6.1.2. Pre-Procedure Exclusion Criteria

Subjects will be excluded from participating in this Study if they meet any of the following exclusion criteria prior to initiation of the endoscopic procedure.

Pre-Operative Exclusion Criteria	1. Medical contraindication to bronchoscopy; 2. Ground glass opacity lesions on pre-procedure CT 3. Participation in any other clinical trial 30 days before and throughout the duration of the study; 4. Uncontrolled or irreversible coagulopathy; 5. Female subjects who are pregnant or nursing or those of child-bearing potential refusing a pregnancy test; 6. CT scan done over a month before the bronchoscopy procedure.

6.1.3. Intra-Operative Exclusion Criteria

Subjects will be excluded from participating in this Study if any of the following exclusion criteria occur during the endoscopic procedure:

Intra-Procedure Exclusion Criteria	Any presenting condition discovered intra-procedurally that in the opinion of the investigator would make participating in this study not in the patient's best interest.

6.2. Withdrawal of Subjects

While study withdrawal is discouraged, patients may withdraw from the study at any time, with or without reason and without prejudice to further treatment. In all cases of withdrawal, the reason(s) for withdrawal (if given) will be recorded upon study termination.

In addition, the investigator may withdraw the subject due to any of the following situations:

- adverse event
- any other reason determined by the investigator to be in the best interest of the subject.

Subjects withdrawn from the Study prior to insertion of the ARES should be converted to conventional bronchoscopy. Subjects withdrawn due to an adverse event should be followed until the event has been resolved or is stable, if at all possible.

7. Written Informed Consent

Written Informed Consent must be obtained for all patients who are potential study candidates before any study-specific tests or procedures are performed.

Patients who meet general entry criteria will be asked to sign the study-specific, Institutional Review Board (IRB) -approved Informed Consent form before any study-specific tests or procedures are performed. Study personnel should explain that even if a patient agrees to participate in the study and signs an informed consent form, the ARES may demonstrate that the patient is not a suitable candidate for the study.

A Screening/Enrollment Log will be maintained to document select information about candidates who fail to meet the entry criteria.

8. Study Procedures and Enrollment

8.1. Duration of Subject Participation

Once the subject has completed 6 weeks (±1 week) follow-up without study related adverse events requiring further follow-up, subject will be exited from the study.

8.2. Enrollment

Subjects that meet the pre-operative inclusion/exclusion criteria will be invited to participate in the Study and sign the IRB approved informed consent form. All subjects must provide written informed consent before undergoing any study related activity.

8.3. Assessment Schedule

The following page outlines the required study assessments.

Table 1. Schedule of Assessments

Test/Parameter	Screening/ Baseline	Pre-Procedure	Procedure	Discharge	Follow-up 24±12 hours	Follow-up 7±3 days	Follow-up 6±1 weeks
Informed Consent	X						
Pregnancy Test (if applicable)	X						
Preliminary Qualification (inclusion/exclusion criteria)	X						
Medical History (pulmonary status)	X						
Physical examination		X				X	
ECG	X						
Blood test and coagulation test (PT/INR)[1]	X						
HRCTScan[2]	X						
Fluoroscopy[3]			X				
Radial probe Endobronchial ultrasound (REBUS) [4]			X[4]				
Chest X-ray[5]				X[5]			
Concomitant medications[6]	X	X					
Follow-up Form				X	X	X	X
Navigation/control evaluation			X				
Biopsy sample evaluation			X				

[1] A blood test including the PT/INR coagulation test will be assessed before the procedure.
[2] The procedure will take place within 30 days of CT scan for participation in the study.
[3] Fluoroscopy will be used in conjunction to provide an additional viewing method during the procedure.
[4] REBUS will be used to confirm the presence of a lesion in patients where additional confirmation is needed.
[5] Chest X-ray within 2 hours from the conclusion of the procedure.
[6] Aspirin and clopidogrel will be stopped one week before procedure. Oral anticoagulants will be stopped at least 5 days before and coagulations tests will be performed before procedure. Anticoagulants will be restarted 24 hours

after procedure if no bleeding persists. Subcutaneous anticoagulants will be stopped 24 hours before and restarted 24 hours after procedure if no bleeding persists.

Informed Consent. A study specific, IRB approved written informed consent must be obtained for all patients who are potential study candidates before any study-specific tests or procedures are performed.

Pregnancy Test (if applicable). If there is the potential for pregnancy, a serum pregnancy test will be conducted before entry into the study.

Preliminary qualification (Inclusion/Exclusion criteria). Principal Investigator is responsible for certifying that key personnel have received adequate training to ensure they are aware of the regulations governing human subjects research and understand and adhere to the IRB-approved research protocol. Compliance with these standards provides assurance that the rights, safety, and well-being of human subjects are protected and the integrity of the data collected. Potential study candidates must meet the study specific Inclusion/Exclusion criteria based on the screening assessment. For the purpose of this study, a peripheral lung lesion is defined as a lesion located in a sub segmental branch of the bronchial tree that it cannot be accessed by convex probe endobronchial ultrasound.

Medical history. During the screening/baseline assessment, the investigator or coordinator will record details of medical history as they relate to pulmonary status.

Physical examination. The investigator will perform a brief, directed physical and pulmonary examination and document any preoperative abnormalities. The examination will be repeated at the day 7 post-procedure.

Electrocardiogram (ECG). Stickers will be placed on each arm and leg and to your chest area and a heart tracing is performed to measure electrical activity of your heart.

Blood tests including the PT/INR coagulation test. These tests may be needed before the procedure to ensure that study patients have no problems related to blood clotting. (see above). Bleeding can sometimes occur after bronchoscopy, especially if tissue samples are taken. The study patients will be asked to stop anticoagulants several days prior to the procedure (see Table 1. above).

HRCT scan. CT analysis will require a full inspiratory CT scan. CT Scans should be performed no longer than 30 days pre-procedure as part of screening assessment. Specific CT parameters for scanner model and manufacturer will be provided to the site. De-identified CT scans may be provided to the study sponsor.

Fluoroscopy. Fluoroscopy will be used in conjunction with the bronchoscopy to provide an additional viewing method during the procedure.

Radial probe endobronchial ultrasound (REBUS). REBUS will be used to confirm the presence of a lesion in patients where additional confirmation may be needed.

Chest X-ray. Patients will undergo a routine chest X-ray within 2 hours from the conclusion of the procedure to o rule out complications such as pneumothorax.

Concomitant Medications. Principal investigator will determine relevant disease/procedure specific concomitant medications that is important for a study conduct. Only the relevant medication will be recorded on a rolling medication log or the relevant case report forms.

Follow-up. The 24 hours (±12 hours) follow-up will be a phone consultation, 7 days (±3 days) follow-up will be an office visit and 6 weeks ((±1 week) follow-up will be a phone consultation. During the follow-up, adverse events will be recorded and associated case report forms will be completed.

Navigation/Control evaluation. The system navigation/control will be evaluated and recorded on the procedure CRFs.

Biopsy sample evaluation. Content and adequacy of biopsy samples will be assessed by pathologist or cytotechnologists using the rapid on-site evaluation (ROSE). A preliminary diagnosis will be recorded. The final histopathologic diagnosis will be recorded on the week 6 follow-up CRF.

8.4. Methods and Procedure

If a technical malfunction of the ARES was to occur, a conventional bronchoscope will be used at the discretion of the investigator. The study procedure may be recorded with an external video camera for educational purposes only.

Bronchoscopy:

Sedation: General anesthesia will be administered by an anesthesiologist per standard care at El Camino Hospital in a dedicated bronchoscopy suite. Patients will be continuously monitored throughout the procedure as per standards practices at El Camino Hospital.

Airway inspection: When adequate sedation has been given, the bronchoscope (BF-P190, Olympus, Tokyo, Japan) will be inserted into the tracheobronchial tree through endotracheal tube and a standard airway inspection will be performed.

Robot-assisted bronchoscopy: Following standard airway inspection, the robotic system will be positioned in an operative position. A study investigator will connect the sterile robotic bronchoscope to the light source and camera box, manually inserted the bronchoscope into the endotracheal tube and attached it to the robot. Then, the investigator will remotely advance the bronchoscope into the bronchial tree using the endoscope controller and will navigate it into the targeted lobar segment using EM navigation. In addition to direct visualization, monoplanar fluoroscopy may be used to provide additional viewing method during all procedures.

REBUS: Once the bronchoscope was positioned within 2 cm from the targeted lesion, REBUS probe will be passed to confirm localization of a targeted lesions. The REBUS images will be recorded and classified as either concentric or eccentric.

TBNA and Biopsy: An aspiration needle will be first inserted into the working channel and advanced along the same pathway to the lesion. Four needle aspirations will be performed from the targeted lesion. Secondly, four biopsies will be performed using forceps and acquired samples will be placed in formalin.

ROSE: Needle aspiration samples will be plated on slides for immediate on-site evaluation by the cytopathology team, as per the standard practice of the Interventional Pulmonology team at El Camino Hospital. Rapid on-site evaluation (ROSE) of acquired cytologic specimen will be performed in all cases.

ROSE diagnostic: If ROSE provides a definitive diagnosis, the procedure will be completed.

ROSE non-diagnostic: If ROSE does not provide a definitive diagnosis, conventional bronchoscopy will be performed.

Conventional Bronchoscopy: In cases in which ROSE using a robotic bronchoscope does not provide a definitive diagnosis, a conventional bronchoscopy using standard EM navigation may be used.

8.5. Post Bronchoscopy

Prior to hospital discharge, all subjects will be evaluated for adverse events. These data will be captured in the Case Report Forms. The patient will be managed post-operative in a dedicated post-procedure area as per standard practices at El Camino Hospital. The subject will be monitored for postoperative symptoms and will undergo a chest X-ray within 2 hours from the conclusion of the procedure, to rule out complications such as pneumothorax. Prior to hospital discharge, the investigator and/or designee will arrange a follow-up appointment.

8.6. Follow-up

The subject will have a follow-up phone call on day 1 post procedure (24 hours ±12 hours), a follow-up appointment in the clinic 7 days post-procedure ± 3 day and the final phone call follow-up 6 weeks ± 7 days post-procedure.

8.7. Study Exit

Once the subject has completed 6 weeks follow-up or has withdrawn, they should be exited from the Study provided they do not have any conditions that require continued follow-up. The date of exit and subject status will be recorded on the Study Completion Form.

9. Assessment of Device Performance

9.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint is the completion of the intended bronchoscopic procedure as defined by the ability to acquire tissue with biopsy tools.

Ability to acquire tissue with biopsy tools: The sum of ARES results that were positive for tissue acquisition divided by the sum of all targets.

9.2. Secondary Effectiveness Endpoints

The following will be considered secondary endpoints:

- Identification of correct bronchi leading to the targeted lesions
- Ability to localize targeted lesion
- Alignment capabilities
- Time to REBUS confirmation (lesion localization), time to the tissue acquisition confirmation, Total procedure time (from introduction to removal of the bronchoscope) and procedure interruptions
- Diagnostic yield
- Conversion to conventional bronchoscopic procedure
- Anesthesia time

Identification of correct bronchi leading to the targeted lesions: The principal investigator will assess the capabilities of the ARES navigation to identify optimal path to the targeted lesion.

Ability to localize targeted lesion: Radial probe endobronchial ultrasound will be used in all cases to confirm the presence of a lesion immediately before performing biopsy.

Alignment capabilities: The sum of ARES results that were positive for the first attempt of tissue acquisition divided by the sum of all attempts.

Time to REBUS confirmation: Is defined by the time the ARES bronchoscope is inserted into the oropharynx until the localization of the targeted lesion is confirmed by REBUS.

Time to the tissue acquisition confirmation: Is defined by the time the ARES bronchoscope is inserted into the oropharynx until the tissue acquisition is confirmed by the ROSE.

Total procedure time: Total procedure time is defined by the time the ARES bronchoscope is inserted into the oropharynx until the time a biopsy tool is removed.

Diagnostic yield: $= \frac{a+b}{n}$ where

- a = the sum of ARES results that were diagnostically positive for malignancy at 6-week follow-up
- b = the sum of the ARES results that were diagnostically negative for malignancy at 6-week follow-up
- n = the sum of all targets

Conversion to conventional bronchoscopic procedure: If ROSE does not provide a definitive diagnosis in 4 attempts, the conventional bronchoscopy will be used to acquire additional specimens.

Number of the procedure converted to the conventional bronchoscopy for any reason.

9.3. Primary Safety Endpoint

Device related adverse events (AEs)

9.4. Secondary Safety Endpoint

Complications unrelated to device.

10.Statistical Considerations

None

11.Data Management – Data Collection and Processing

Standardized CRFs will be utilized by participating site using a standardized database. Conventional paper-based CRFs will be used and send to a sponsor designee via secure encrypted emails. Investigator is responsible for the accurate completion and timely submission of the data collected during the Study. Incoming data will be monitored by the sponsor or designee to identify inconsistent or missing data and any adverse events. Any data issues are to be promptly addressed with the investigator. Quality assurance procedures will be established to ensure that complete, accurate and timely data are submitted, that protocol requirements are followed and that complications, adverse events and adverse device effects are correctly reported and investigated, as appropriate. Investigator is to maintain all source documents as required by the protocol, including laboratory results, supporting medical records, and signed Informed Consent forms. The source documents will be used during the regular monitoring visits to verify information from the database against data contained on the completed CRFs.

The Principal Investigator must maintain detailed records on all subjects who sign the Informed Consent and begin the pre-procedure evaluation. Data for enrolled subjects will be entered into CRFs provided by the Sponsor. All data should be entered completely, promptly and legibly. For source documents, corrections should be made in a manner that does not obscure or eliminate the original error, by striking through the original data with one line, and initialing and dating the change, along with the reason for the change (if not obvious).

Study Exit CRFs are completed for all enrolled subjects, regardless if they did or did not complete the Study (e.g., subject discontinuation, Study termination).

12.Monitoring Procedures

12.1. Monitoring

Monitoring visits to the clinical sites will be made periodically during the study by the Sponsor's designee to ensure that all aspects of the current, approved protocol/amendment(s) are followed. Original source documents will be reviewed for verification of data in the database. The Investigator/institution guarantees direct access to

original source documents by Auris Surgical Robotics, Inc. personnel, their designees, and appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a patient that is seen by a non-study physician at a non-study institution, photocopies of the original source documents must be made available for review.

It is important that the Investigator and relevant study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

Phone contacts and site visits will be conducted to ensure that the protocol is being followed and that any protocol deviations are properly documented. Clinical monitoring will include a verification that Informed Consent was properly obtained for all enrolled study participants, a review of clinical records for accuracy and completeness, resolution of missing or inconsistent results and a review of source documents. The clinical monitor will verify that the Case Report Forms (CRFs) are in agreement with the source documentation and other records. The investigator will make available to the clinical monitor for review all Informed Consent documents, source documentation, original laboratory data and other relevant records for all enrolled subjects at the site. It is important that the investigator and other relevant site personnel are available for consultation with the clinical monitors during the monitoring visits and that sufficient time is devoted at the site to the monitoring process.

Additionally, telephone and/or e-mail contact will be conducted on a regular basis with the investigator and the site staff to ensure that the protocol is being followed and to address any issues that may occur during the course of the Study.

If a deficiency is noted during an on-site visit (or at any other time during the course of the Study), the clinical monitor is required to discuss the situation with the investigator and the Sponsor (if required) to secure compliance.

12.2. Device Distribution and Accountability

12.2.1. Device Distribution

Auris Robotic Endoscopy System (ARES) for Bronchoscopy will be provided free of charge to the investigator for his exclusive use in this NSR study.

12.2.2. Device Accountability

Auris Surgical Robotics will maintain device accountability as required for this NSR Study.

12.2.3. Return of Materials Upon Study Termination

The Auris Robotic Endoscopy System (ARES) for Bronchoscopy will be returned at the end of the study.

13.Quality Control and Quality Assurance

13.1. Site Training

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will provide instructional material to the Study sites, as appropriate;

- Instruct the Investigators and Study personnel on the protocol, the completion of the CRFs, and Study procedures
- Communicate regularly with site personnel via mail, email, telephone, and/or fax
- Make periodic visits to the Study sites.

During those visits, the sponsor's designee will monitor the subject data recorded in the CRFs against source documents at the Study site.

13.2. Physician Training

Prior to enrolling subjects in the Study, investigators will be provided didactic training on the procedural steps required to use the ARES system. Physicians who have not previously used the device will receive training with a Sponsor-designated proctor using a benchtop model to simulate the use of the ARES system.

13.3. Audits and Inspections

The Principal Investigator for the site will inform the Sponsor or the Sponsor's designee in advance if they are to be audited or inspected by any regulatory agencies. The Sponsor or the Sponsor's designee will also inform the site if they are made aware of a pending audit or inspection by a regulatory agency. No FDA inspections are expected to be associated with this NSR Study.

14.Adverse Events

14.1. General

All adverse events (AE) and serious adverse events (SAE) will be monitored from the time of enrollment through the end of follow-up.

An AE is defined as any undesirable clinical occurrence in a patient whether or not it is considered to be device related. In addition, the definition of AE applies to any event with an onset post study procedure or to any underlying diseases, present at baseline, that exacerbate in severity post study procedure. Therefore, an underlying disease that was present at the time of enrollment is not reported as an AE, but any increase in the severity of the underlying disease is to be reported as an AE. All reported AEs must be recorded in the database. A description of the event, including the start date, resolution date, action taken, and the outcome should be provided, along with the Investigator's assessment of the relationship between the AE, the study treatment and the study procedure.

The following definitions for rating severity of adverse events will be used:

Mild: Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs or symptoms are transient.

Moderate: Interferes with the subject's usual activity and/or requires symptomatic treatment.

Severe: Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

A serious adverse event (SAE) is defined as an event which leads to:

- Death due to any cause
- Life-threatening condition
- Results in persistent or significant disability/incapacity
- Requires in-patient hospitalization or prolonged hospitalization
- Necessitates an intervention to prevent a permanent impairment of a body function or permanent damage to a body structure
- Results in congenital abnormality

All SAE's will be reported.

***Device-Related Adverse Event**:* an adverse event is considered to be device-related when, in the judgment of the Investigator, the clinical event has a reasonable time sequence associated with use of the **AURIS ROBOTIC ENDOSCOPY SYSTEM (ARES)** and is unlikely to be attributed to concurrent disease or other procedures or medications. It is reasonable to believe that the system directly caused or contributed to the adverse event.

***Procedure-Related Adverse Event**:* an adverse event is considered to be procedure-related when, in the judgment of the Investigator; it is reasonable to believe that the event is associated with the assigned study procedure and is not specific to the **AURIS ROBOTIC ENDOSCOPY SYSTEM (ARES)** used. Other products, surgical techniques, or medications required specifically for the procedure are likely to have contributed to the occurrence of the event.

Concomitant Medication-Related Adverse Event: an adverse event is considered to be concomitant medication related when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with concomitant medications used in conjunction with the **AURIS ROBOTIC ENDOSCOPY SYSTEM (ARES)** and is not otherwise specific to the **AURIS ROBOTIC ENDOSCOPY SYSTEM (ARES)** (e.g. bleeding associated with anticoagulation medication).

Pre-Existing Condition-Related Adverse Event: an adverse event is considered to be related to a pre-existing condition when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with the subject's pre-existing condition and is not specific to the **AURIS ROBOTIC ENDOSCOPY SYSTEM (ARES)** or procedure. Pre-existing conditions that are aggravated or become more severe during or after the procedure should be evaluated on a case-by-case basis to

determine if the event may be more appropriately classified as device-related or procedure-related.

Auris Surgical Robotics, Inc., or its designee, in cooperation with the Investigator, will assess all adverse events considered to be device-related for potential reportability to the FDA and other regulatory authorities as an Unanticipated Adverse Device Effect (UADE).

The Investigator should follow all unresolved serious adverse events until the events are resolved, the subject is lost to follow-up, the subject has withdrawn consent, or the adverse event is otherwise explained.

For purposes of this study, the following events are not likely to be device-specific adverse events, because they are typical procedure/anesthesia related adverse events normally expected to occur in conjunction with these types of bronchoscopic procedures / post-procedure, or are associated with customary, standard care of subjects undergoing these procedures:

- Any pre-planned surgical procedures
- Bleeding
- Pneumothorax
- Post-procedure respiratory insufficiency

This listing of events is intended to provide guidance to the investigational sites for purposes of adverse event reporting. The Investigator at the investigational site should utilize his/her own clinical judgment in evaluating adverse experiences, and may decide that the above events should be reported as adverse events.

14.2. Reporting of Serious and Non-Serious Adverse Events

14.2.1. General Reporting Requirements (Serious & Non-Serious Adverse Events)

All serious and potentially device- and/or procedure-related adverse events must be recorded on the Adverse Event CRF by the Investigator (or designee). The report should include: severity, duration, action taken, treatment outcome and relationship of the adverse experience to the study device, procedure, concomitant medications, pre-existing condition, etc. (i.e., unrelated, related or relationship unknown).

In the case of serious adverse events, procedure and/or device observations and malfunctions, medical record documentation (e.g. procedure notes, operative notes, discharge summary, relevant progress notes, imaging or lab studies) must be provided to Auris or its designee.

The following criteria must also be adhered to by the Investigator in the case of serious adverse events:

- The Adverse Event CRF must be signed by the Investigator or Co-Investigator.
- It is the responsibility of the Investigator to inform their IRB of serious adverse events as required by their IRB procedures and in conformance with FDA and local regulatory requirements.

All serious adverse events must be reported by the Investigator (or designee) to the sponsor, within 24 hours of learning of the adverse event via CRF. The Auris contact information for questions is:

14.3. Device Failures and Malfunctions

All reported device observations, malfunctions or failures of the Auris ARES are required to be documented in the CRF. Device failures and malfunctions should also be documented in the patient's medical record.

NOTE: Device failures or malfunctions are NOT to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded in the usual way.

15.Ethical Considerations

15.1. Study Conduct & the Declaration of Helsinki

The Study will be performed in accordance with the relevant parts of Title 21 CFR Parts 812, 50, 54, 56 and ISO 14155-1 / 14155-2.1; the ICH Guidelines for Good Clinical Practices (E6), the Declaration of Helsinki, and any regional and/or national regulations.

15.2. Institutional Review Board/Ethics Committee

A copy of the protocol, proposed Informed Consent form, other written patient information and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written IRB approval of the protocol and Informed Consent form must be received by Auris Surgical Robotics, Inc. before recruitment of patients into the study and shipment of product.

The Investigator must submit and, where necessary, obtain approval from the IRB as well as the FDA, for all subsequent significant protocol amendments and significant changes to the Informed Consent form. The Investigator should notify the IRB of deviations from the protocol or SAEs and UADEs occurring at the site and other SAE/UADE reports received from Auris Surgical Robotics, Inc in accordance with local procedures.

The Investigator will be responsible for obtaining annual IRB approval and renewal throughout the duration of the study. Copies of the Investigator's reports and the IRB continuance of approval must be sent to Auris Surgical Robotics, Inc.

15.3. Informed Consent Form

A sample Informed Consent form is provided in Section 21 Attachment 2 for the Investigator to prepare for use at his/her site. The written Informed Consent documents should be prepared in the language(s) of the potential patient population.

The reviewing IRB and the sponsor must first approve the Informed Consent forms that are used. The Informed Consent forms that are used should be in accordance with the current guidelines as outlined by the Good Clinical Practices (GCP) guidelines, Declaration of Helsinki and the International Conference on Harmonization (ICH).

Prior to participation in the clinical Study, each patient must give written Informed Consent after the context of the study has been fully explained to the patient in language that is easily understood by the patient. The patients must also be given the opportunity to ask questions and have those questions answered to their satisfaction.

Written Informed Consent must be recorded appropriately by means of the patient's, or their legal representative's dated signature. The patient will receive a copy of the Informed Consent form.

15.4. Amending the Protocol

An Investigator may not make protocol changes without prior approval by Auris Surgical Robotics. All significant protocol changes that may affect the following must be submitted and approved by the IRB before initiating the change:

- validity of the data or information resulting from the completion of the approved protocol;
- relationship of the likely subject risk to benefit relied upon to approve the protocol;
- scientific soundness of the investigational plan, or;
- rights, safety, or welfare of the human subjects involved in the investigation.

Auris will submit a copy of the protocol amendment to the Investigator for his IRB to review. The investigative site must send Auris Surgical Robotics a copy of the IRB approval letter for the protocol amendment.

Auris may make certain administrative changes to the protocol without prior approval of the IRB. The site IRB will be notified of these changes.

15.5. Emergency Actions

Auris Surgical Robotics, Inc accepts the right of the Investigator to deviate from the protocol in an emergency when necessary to safeguard the life or the physical well-being of a study patient. The Investigator must give notice of any emergency deviations and justification for the deviation to Auris Surgical Robotics, Inc and the IRB as quickly as possible after the episode, in any event no later than 24 hours after the emergency.

15.6. Protocol Deviations

A protocol deviation is defined as an event where the Clinical Investigator or site personnel did not conduct the study according to the protocol.

Investigators shall be required to obtain prior approval from Auris management before initiating deviations from the protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval shall be documented in writing and maintained in clinical study management and Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g. subject was not available for scheduled follow-up office visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation and will be reported via the appropriate CRF.

Deviations must be reported to Auris regardless of whether medically justifiable, pre-approved by Auris or taken to protect the subject in an emergency. Subject specific deviations will be reported on the Protocol Deviation case report form. Non-subject specific deviations, (e.g. unauthorized use of an, **AURIS ROBOTIC ENDOSCOPY SYSTEM (ARES)** device outside the study, unauthorized use of an **AURIS ROBOTIC ENDOSCOPY SYSTEM (ARES)** device by a physician who has not signed an Investigator agreement or not been trained in the use of the device, etc.), will be reported to Auris reported via the appropriate CRF. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB reporting policies and procedures.

Regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the protocol. For reporting purposes, Auris classifies study deviations as major and minor:

*Major deviation***:** Any deviation from subject inclusion and exclusion criteria, subject informed consent procedures or unauthorized device use.

*Minor deviation***:** Deviation from a protocol requirement such as incomplete/inadequate subject testing procedures, follow-ups performed outside specified time windows, etc. Minor Deviations that continue to occur at an investigational site may be classified as Major Deviations if corrective action is not taken to secure future compliance to the protocol.

15.7. Coverage of Expenses

The treated subjects will not be reimbursed or compensated for participating in the Study.

15.8. Confidentiality

Confidentiality of subjects will be maintained throughout the Study. A unique identification code will be assigned to each subject participating in this Study. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity. The Sponsor will make every reasonable effort to protect the confidentiality of the subjects participating in the Study.

16.Study Administration

Auris Surgical Robotics, Inc. in cooperation with the Investigator will make necessary efforts to ensure that this study is conducted in compliance with GCPs and all applicable regulatory requirements.

16.1. Pre-Study Documentation Requirements

Prior to shipment of product, the following documents must be provided to Auris Surgical Robotics, Inc:

- Signed and dated Investigator Agreement
- A copy of the written IRB approval of the protocol
- A copy of the written IRB approval of the Informed Consent Form
- A copy of the curriculum vitae of the Principal Investigator and Co-Principal Investigator (if applicable)

16.2. Source Documentation

The Principal Investigator must maintain detailed source documents on all Study subjects who are enrolled in the Study or who undergo screening. Potential source documents include subject medical records including: hospital charts, clinic charts, Investigator's subject Study files, as well as the results of diagnostic tests (e.g., laboratory tests).

The following minimum information should be recorded in the subject's medical records:

- The date the subject entered the Study and the subject number
- The Study protocol number and the name of the Sponsor
- The date that informed consent was obtained
- Evidence that the subject meets Study eligibility requirements (e.g., medical history, Study procedures and/or evaluations)
- The dates of all Study related subject visits
- Evidence that required procedures and/or evaluations were completed
- Use of any concurrent medications
- Documentation of specific device used, if any
- Occurrence and status of any Adverse Events
- The date the subject exited the Study, and a notation as to whether the subject completed the Study or was discontinued, including the reason for discontinuation.

16.3. Record Retention

The Investigator will maintain all essential Study documents and source documentation, in original format, that support the data collected on the study patients in compliance with the ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will

be retained for a longer period of time by agreement with Auris Surgical Robotics, Inc or in compliance with other regulatory requirements. When these documents no longer need to be maintained, it is Auris's responsibility to inform the Investigator. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility. Auris Surgical Robotics, Inc must receive written notification of this custodial change.

16.4. Criteria for Terminating Study

Auris Surgical Robotics, Inc reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of patients. Investigators and associated IRB will be notified in writing in the event of termination.

Possible reasons for study termination include:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- A decision on the part of Auris Surgical Robotics, Inc to suspend or discontinue development of the device.

16.5. Criteria for Suspending/Terminating a Study Center

Auris Surgical Robotics, Inc reserves the right to stop the study center at any time after the study initiation visit if no patients have been enrolled or if the center has multiple or severe protocol violations without justification or fails to follow remedial actions.

Possible reasons for suspending/terminating a study center include:

- Repeated failure to complete case report forms prior to scheduled monitoring visits.
- Failure to obtain written Informed Consent.
- Failure to report CEC Events/SAE/UADE to Auris Surgical Robotics, Inc. within 24 hours of knowledge.

16.6. Investigator Responsibilities

- Agree to sign and adhere to the Investigator Agreement
- Agree to participate in Investigator meetings as scheduled by Auris Surgical Robotics, Inc
- Be willing to provide required assessments for analysis
- Be willing to perform and be capable of performing treatment procedures as outlined in this protocol
- Comply with all required elements of this protocol (e.g., perform testing and follow-up as specified, especially during personnel transitions) and supply material suitable for quantitative analysis

- Agree to obtain written Informed Consent before any study specific procedures are performed in accordance with GCP
- Complete all CRFs prior to scheduled monitoring visits
- Be willing to change hospital routine if required by protocol (as long as patient safety and well-being is not compromised)

17.Publication Policy

The existence of this clinical Study is confidential, and it should not be discussed with persons outside of the Study. Additionally, the information in this document and regarding this Study contains trade secrets and commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by regional or national law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in the Study who have a need to know, but all such persons must be instructed not to further disseminate this information to others. These restrictions of disclosure will apply equally to all future information provided that is indicated as confidential.

The data generated by this clinical Study are the property of the Sponsor, Auris Surgical Robotics, Inc., and should not be disclosed without their prior written permission. These data may be used by the Sponsor now and in the future for presentation or publication at Sponsor's discretion or for submission to governmental regulatory agencies. The Principal Investigators may publish or present the Study results with prior consent of the Sponsor, but will not disclose confidential information. Prior to submission by a Principal Investigator for publication or presentation, the Sponsor will be provided with the opportunity to review the submission for confidential information and accuracy.

18.Regulatory Considerations

18.1. Role of Auris Surgical Robotics

As the sponsor of this clinical study, Auris has the overall responsibility for the conduct of the study, including assurance that the study meets all applicable regulatory requirements of the Food and Drug Administration (FDA). In this study, Auris may have certain direct responsibilities and may delegate other responsibilities to Consultants. Together, both Auris and its Consultants will ensure adherence to the sponsor's general duties. These regulations may include applicable portions of: (21 CFR 812.40), selection of Investigators (21 CFR 812.43), monitoring (21 CFR 812.46), supplemental applications (21 CFR 812.35 (a) and (b)), maintaining records (21 CFR 812.140 (b)), and submitting reports (21 CFR 812.150 (b)).

Sponsor may choose to appoint a steering committee for the study; this committee may include investigators, other experts not otherwise involved in the trial, and representatives of the sponsor. A sponsor may delegate and/or seek advice from trial steering committee members about study design, ongoing monitoring of study conduct

and adjudication of individual adverse events. In addition, the trial steering committee members may be asked to participate in the analysis and/or interpretation of data as well as to revise manuscript(s) before submission.

18.2. General Duties [21 CFR 812. 40]

No IDE application to FDA is required for this NSR Study. The Sponsor and the Investigator are responsible for obtaining IRB approval prior to start of the study. As the sponsor, Auris is also required to obtain signed study agreements, to provide the Investigators with the information necessary to conduct the study and adequate on-site training to conduct the Study, to ensure proper clinical site monitoring, and to provide the required reports to the Investigators, and IRBs.

Auris will be responsible for providing quality data that satisfies publication requirements and informing of serious unanticipated adverse events and deviations from the protocol.

18.3. Monitoring [21 CFR 812. 46]

Sponsor will conduct investigational site monitoring to ensure that all Investigators are in compliance with the protocol and the Investigators' agreements. The sponsor and/or designee will monitor the sites to ensure that the completed Case Report Forms match the medical records, and resolve any differences. The sponsor will retain the right to remove either the Investigator or the investigational site from the study.

The sponsor will review significant new information, including unanticipated serious adverse events and ensure that such information is provided to the Investigators and to all reviewing IRB's.

18.4. Supplemental Applications [21 CFR 812. 335 (A) and (B)]

As appropriate, the sponsor will submit changes in the Investigational Plan to the Investigators to obtain IRB re-approval. No FDA submissions are required.

18.5. Maintaining Records [21 CFR 812. 140 (B)]

The sponsor will maintain copies of correspondence, data, shipment of devices, serious adverse device effects and other records related to the clinical Study. The sponsor will maintain records related to the signed Investigator Agreements.

18.6. Submitting Reports [21 CFR 812. 150 (B)]

No FDA submissions are required for the NSR Study.

18.7. Site Record Retention Policy [21 CFR 812. 140 (D)]

The sponsor and clinical sites will maintain all records pertaining to this study for a period of two years following: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a pre-

market approval application. Record retention dates will be provided to all concerned by the sponsor.

18.8. Informed Consent & Institutional Review Board (IRB) [21 CFR Parts 50 & 56]

All subjects must provide written informed consent in accordance with the local clinical site's IRB. A copy of the consent form from each center must be forwarded to the Sponsor for review and approval prior to submitting it to the IRB. The site must provide the Sponsor with a copy of the clinical site's IRB approval letter and the informed consent. Yearly approvals for the continuation of the Study at each clinical site must also be forwarded to the Sponsor.

All Protected Health Information (PHI) to be collected in the study will be described in the informed consent form, and all study data will be managed in accordance with the Privacy Law (HIPAA).

19.Abbreviations and Definitions

19.1. Abbreviations

ACT	Activated clotting time
AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CV	Curriculum Vitae
FDA	Food and Drug Administration
Hgb	Hemoglobin
Hct	Hematocrit
IFU	Instructions for Use
IRB	Institutional Review Board
MDR	Medical Device Reporting
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Event

19.2. Definitions

ADVERSE EVENT SEVERITY RATING

Mild: Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms

would not require medication or a medical evaluation; signs or symptoms are transient.

Moderate: Interferes with the subject's usual activity and/or requires symptomatic treatment.

Severe: Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

APPROVAL (IN RELATION TO INSTITUTIONAL REVIEW BOARDS (IRBs)
The affirmative decision of the IRB that the clinical investigation has been reviewed and may be conducted at the institutional site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

CO-INVESTIGATOR / SUB-INVESTIGATOR
Any individual member of the clinical investigation team designated and supervised by the Investigator at an investigational site who performs critical investigation-related procedures and/or makes important investigation-related observations. See also Investigator.

CONFIDENTIALITY
Prevention of disclosure, to other than authorized individuals, of a Sponsor's proprietary information or of a subject's identity / Protected Health Information (PHI) in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

DEVICE FAILURE / MALFUNCTION
The device does not perform in accordance with the IFU.

CASE REPORT FORM (CRF)
A document designed to record all of the protocol-required information to be reported to the Sponsor on each subject.

INFORMED CONSENT
A process by which a subject voluntarily confirms in writing his or her willingness to participate in a particular investigation, after having been informed of all aspects of the investigation that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated Informed Consent form.

INVESTIGATIONAL SITE
The location(s) where investigation-related activities are actually conducted.

INVESTIGATOR
The person responsible for the conduct of the clinical investigation at an investigational site. If an investigation is conducted by a team of individuals at an investigational site,

the Investigator is the responsible leader of the team and may be called the Principal Investigator. See also Co-Investigator.

SERIOUS ADVERSE EVENT (SAE)
Any untoward medical occurrence that results in death, is life threatening, requires subject hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity.

SUB-INVESTIGATOR / CO-INVESTIGATOR
Any individual member of the clinical investigation team designated and supervised by the Investigator at an investigational site who performs critical investigation-related procedures and/or makes important investigation-related observations. See also Investigator.

SUBJECT
An individual who participates in a clinical investigation.

UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE)
Any serious adverse effect on health or safety or any life-threatening problem or death *caused by, or associated with the study device,* if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the Investigational Plan or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

19.3. Bibliography

1 Jemal A, Siegel R, Xu J, Ward E. Cancer Statistics 2010. Ca Cancer, J Clin 2010;60:277–300.

2 Aberle R, Adams AM, Berg CD, et al. National lung screening trial research team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395–409.

3 Gilbert C, Akulian J, Ortiz R, Lee H, Yarmus L. Novel bronchoscopic strategies for the diagnosis of peripheral lung lesions: present techniques and future directions. Respirology. 2014 Jul;19(5):636-44.

20.Attachment 1: Investigator Responsibilities, Records and Reports

20.1. Investigator Responsibilities

The investigator is responsible for ensuring that this Study is conducted according to this protocol and that signed Informed Consent is obtained from each subject prior to their inclusion in this Study.

It is the investigator's responsibility to ensure that all staff assisting with this Study have the appropriate qualifications and are fully instructed on the Study procedures and RPN subject confidentiality, as specified in the Investigator Agreement with the Sponsor.

The investigator is responsible for ensuring that the conduct of the Study conforms to the IRB requirements and provides all necessary communication with the IRB including, but not limited to, annual Study reports and required adverse event notifications.

20.2. Investigator Records

Case Report Forms

The standardized Case Report Forms (CRFs) will be used to collect complete and accurate records of the clinical data from the Study according to the Good Clinical Practice (GCP) requirements. The investigator is responsible for collecting and accurately recording the data generated for this Study.

Screening Log

Investigators will maintain a screening log that will record the date of informed consent, the date of screening, the enrollment status (enrolled/excluded) and the reason for exclusion for all screen failures.

20.3. Investigator Reports

Final Study Report

A summary of the final report will be prepared and provided to each Principal Investigator for submission to their respective IRB after completion of the Study.

Serious Adverse Events (SAEs)

The investigators will report by CRF any SAEs including serious, and/or potentially device- or procedure-related adverse events as soon as possible, within 24 hours of the investigator becoming aware of the event, to the Sponsor and to the IRB as per the committee's reporting requirements. The Serious Adverse Event CRF is to be completed and submitted to the Sponsor as initial notification.

Device Malfunctions

The investigators will report by telephone, email or fax any Device Malfunctions as soon as possible, within 24 hours of the investigator becoming aware of the event, to the Sponsor.

WITHDRAWAL OF APPROVAL

If an IRB withdraws the approval to conduct this Study for any reason, the investigator will notify the Sponsor as soon as possible, but in no event later than five working days after the withdrawal of the approval.

21.Attachment 2: Sample Informed Consent Form

22.Attachment 3: Instructions For Use (IFU)

23.Attachment 4: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote RPN for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be RPNed.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing Studies. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to

the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be RPNed. Every precaution should be taken to RPN the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.