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A Prospective, Randomized, Controlled, Multi-Center Evaluation of a Powered Vascular Stapler in Video-Assisted Thoracoscopic Lobectomies

Protocol #: ESC-15-001

Document	Effective Date
Original	November 11, 2015

Sponsor:

Ethicon Endo-Surgery, Inc.
4545 Creek Road
Cincinnati, OH 45242

CONFIDENTIALITY STATEMENT

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by federal or state 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 on disclosure will apply equally to all future information supplied to you which is indicated as privileged or confidential.

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Protocol Number: ESC-15-001

Approval:

Elliott Fagelman, MD
Franchise Medical Director, Ethicon

11/16/15
Date

COMPLIANCE STATEMENT

This study will be conducted in compliance with Good Clinical Practice (and in accordance with the Declaration of Helsinki) as well as all applicable local regulations.

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INVESTIGATOR SIGNATURE

I have read, understood, and agree to:

- Ensure that the requirements for obtaining informed consent are met;
- Conduct the study in accordance with this protocol, including applicable local laws and regulations;
- Maintain the confidentiality of all information received or developed in connection with this protocol;
- Report all serious adverse events as soon as possible, but no later than 24 hours after becoming aware of the event;
- Adhere to the publication policy, as stated in the Clinical Study Agreement, for data collected during this study; and
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting the above commitments.

I will ensure that the Institutional Review Board (IRB)/Ethics Committee (EC) review complies with governmental requirements and will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB/EC all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without sponsor and IRB/EC approval of an amended protocol, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligation of clinical investigators and all other pertinent requirements of the sponsor and government agencies.

_____ _____

Investigator Signature Date

_____

Printed Name of Investigator

SYNOPSIS

Regulatory Classification:	Class II Staple Implantable; Stapler, Surgical 21CFR 878.4750. Cleared 11/24/2014, 510(k) # K141952 CE Mark granted 02/27/2015, Certificate, G7 15 02 57666 049
Indication:	The ECHELON FLEX™ Powered Vascular Stapler (PVS) with Advanced Placement Tip and its reloads are intended for transection and resection of tissue and vasculature. The instruments have application in multiple open or minimally invasive general, gynecologic, urologic, thoracic, and pediatric surgical procedures. The device will be utilized as described in the instruction for use (IFU).

Objective/Endpoint:	The primary objective of the study is to demonstrate that the frequency of hemostatic interventions/procedures required intra-operatively or post-operatively related to the transection of the pulmonary artery (PA) and pulmonary vein (PV) during VATS lobectomy with PVS is not increased when compared to standard of care (SOC). The primary performance endpoint will be: Incidence of hemostatic interventions/procedures completed for intra-operative bleeding related to the transection of the PA and PV during VATS lobectomy with the use of standard of care stapler (SOC) or powered vascular stapler (PVS) defined as: • Hemostasis intervention: bleeding detected and controlled intra-operatively (additional stapling, over-sewing, clip placement, compression, use of suture, sealant, and/or buttress, and/or use of energy); or bleeding that occurs intra-operatively requiring blood or blood product transfusion or an additional surgical procedure (e.g. conversion to open). No hemostasis intervention is defined as no bleeding at the staple line or bleeding that stops after initial blotting of staple line. The primary safety endpoint will be: Incidence of hemostatic interventions /procedures completed for post-operative bleeding related to the transection of the PA and PV during VATS lobectomy with the use of SOC or PVS: • Hemostasis intervention: bleeding that occurs post-operatively requiring blood or blood product transfusion or an additional surgical procedure (related to PA and PV transection). No hemostasis intervention is defined as no interventions needed for post-operative bleeding (related to PA and PV transection).

Study Design:	This prospective, randomized, controlled, multi-center study will collect and compare data from the surgeon's current SOC stapler (for PA/PV transection) and powered vascular stapler.
Number of Subjects (Planned):	Approximately 200 subjects will be randomized
Diagnosis/Criteria for Inclusion:	Subjects satisfying the following criteria will be eligible for participation in this study: 1. Subjects with a confirmed or suspected diagnosis of stage IA to stage IIIA non-small cell lung cancer scheduled for a lobectomy (Lung Cancer Staging per American Joint Committee on Cancer,7th Edition)[5]; 2. Subjects scheduled for VATS lobectomy in accordance with their institution's SOC; 3. Performance status 0-1 (Eastern Cooperative Oncology Group classification); 4. ASA score $\leq$ 3; 5. No prior history of VATS or open lung surgery (on the lung in which the procedure will be performed); 6. Willing to give consent and comply with study-related evaluation and treatment schedule; and 7. At least 18 years of age.
Diagnosis/Criteria for Exclusion:	Subjects will be excluded from the study for any of the following: 1. Prior chemotherapy or radiation (within 30 days prior to the procedure or the duration of the subject's enrollment); 2. Pregnancy; 3. Physical or psychological condition which would impair study participation; or 4. The subject is judged unsuitable for study participation by the Investigator for any other reason.
Finished Product:	ECHELON FLEX™ Powered Vascular Stapler with Advanced Placement Tip

Statistical Methods:	Summary statistics and 95% confidence intervals will be provided for the number and frequency of interventions for the set of SOC and PVS subjects separately. This will be performed based on the total number of firings. An intervention is defined as any firing which is classified as hemostasis intervention. Given that it is expected to have at least 260 firings in each group, the sample size of approximately 200 subjects is considered adequate for descriptive summarization of the number and frequency of surgical interventions. Assuming an approximate background intervention rate of 6%, the given sample size will provide reasonable precision in the estimation of the intervention rate to an expected margin of error for a 95% confidence interval of at most 2.9% for each group. To establish that the intervention rate is not increased compared to SOC, a 95% confidence interval for the difference in proportion of firings requiring interventions for PVS minus SOC will be calculated and powered vascular stapler will be considered to have acceptable performance if the upper bound of the 95% confidence interval does not exceed 3%. The number and percentage of subjects requiring hemostasis interventions post-operatively that are classified as related to SOC or PVS for PA/PV transection (e.g. need for blood product transfusion or additional surgical procedure) will be summarized for each group as a primary safety endpoint. Additional endpoints will be summarized with descriptive statistics and 95% confidence intervals as appropriate for continuous or categorical measurements. Safety will be assessed through the incidence of AEs and serious adverse events (SAEs), which will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

SCHEDULE OF EVENTS

Study Activity	Visit 1	Visit 2	Visit 3	Visit 4
	Screening	Procedure	Post-Op through Discharge	4 week follow-up[e] (post procedure)
Informed consent	X			
Demographic information	X			
Relevant medical/surgical history	X	X		
Inclusion/Exclusion Criteria	X	X		
Pain medication usage[a,d]	X	X	X	X
ASES Standardized Shoulder Assessment	X		X	X
Pain score assessment (incisional, trocar, chest tube pain)			X	X
ASA score		X		
Collection of procedure data[b]		X		
Randomization (SOC or PVS)		X		
Intra-operative interventions on PA/PV		X		
Post-operative interventions on PA/PV			X	X
Procedure duration		X		
Daily volume and characteristics of chest tube(s) drainage			X	X[g]
Concomitant procedures/interventions, if applicable			X	X
Surgeon questionnaires[c]		X		
Date of hospital admission		X		
Overall Operating Room (OR) time		X		
Adverse Events		X	X	X
Anticoagulants[f]	X			
Concomitant medications associated with adverse events/pain		X	X	X
Date(s) of chest tube(s) removal			X	X[g]
Discharge date			X	
Subject exited from study				X

a. Two weeks prior to screening visit through study conclusion
b. See section 4.7.3.1.2 for specific details
c. Surgeon Device Questionnaire (***PVS procedures only***). Surgeon Satisfaction and SURG-TLX ***(SOC and PVS procedures)***
d. Including pain medications given perioperative (i.e. spinal block, intercostal nerve blocks, etc.) and post-operative pain medications
e. Phone call or office visit
f. Anticoagulants taken preoperatively (up to 30 days prior to Visit 2/Procedure), including the stop date
g. If applicable

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ETHICS

Institutional Review Board/Ethics Committee

Participating investigators will ensure that this protocol, Informed Consent Document (ICD), ICD or protocol amendments, and if applicable, any other written information provided to the subjects that assist in the decision to participate are reviewed by an Institutional Review Board (IRB) or Ethics Committee (EC) that complies with governmental requirements. The approving IRB/EC will be responsible for the initial and continuing review and approval of this clinical investigation. Participating investigators will be required to promptly report to the IRB/EC as required by the IRB/EC's policies. Additionally, investigators will be required to refrain from making any changes in the clinical investigation plan without Sponsor and IRB/EC approval of an amended protocol, except where necessary to eliminate apparent immediate hazards to study subjects or others.

Applicable Regulations

This study will be conducted in compliance with Good Clinical Practice and in accordance with the Declaration of Helsinki, ISO 14155: 2011, as well as any other applicable local and country regulatory requirements.

Subject Information and Consent

Regulations concerning the protection of subjects require that informed consent be obtained before a subject may participate in any clinical investigation.

An IRB/EC approved informed consent must be sought from each subject and must be appropriately documented in the subject's medical record prior to initiating the study. It is the Investigator's responsibility to obtain written informed consent from the subject, the Investigator may delegate this responsibility if appropriately documented.

The informed consent process involves the following: giving a subject adequate information concerning the study, providing adequate time for the subject to consider all available options, responding to the subject's questions, ensuring that the subject has comprehended this information and finally, obtaining the subject's written consent to participate in this study. All subjects in this study should be completely informed about the purpose, risks, benefits, and other pertinent details of this study. The informed consent process is careful to avoid the perception of any coercion or undue influence on, or inducement of, the subject to participate, and does not waive or appear to waive the subject's legal rights. The ICD is presented in native, non-technical language that is understandable to the subject.

Prior to a subject's participation in this study, an ICD will be signed and dated by the subject and person who conducted the consent discussion. The subject will be provided a copy of the signed ICD. The ICD and any other written materials provided to the subject to assist in the decision to participate must be revised whenever new information becomes available that may be relevant to their willingness to participate or continue participation in this study. Revision to the ICD and other written materials will receive IRB/EC approval before implementation. Each subject will be required to sign any amended ICD (as required by the IRB/EC) and will receive a copy of the signed ICD.

ADMINISTRATIVE REQUIREMENTS

This study is sponsored by Ethicon Endo-Surgery, Inc. (EES, Cincinnati, OH, USA) and will be conducted in approximately six surgery centers in the United States and/or European Union under a single protocol approved by each participating site's IRB/EC prior to implementation. The principal investigator at each study site is a surgeon qualified by education, experience, and training to perform the study procedure and to assume responsibility for the conduct of this study.

The Data Management and Biostatistics groups of Ethicon Endo-Surgery, Inc.'s Global Surgery Clinical Development will be responsible for the analysis of data from this protocol. An Electronic Data Capture (EDC) system will be utilized by study site personnel to transfer study data from source records (the first point of clinical data capture) onto common electronic case report forms (eCRFs). This system is a web-based, secure electronic software application (Medidata® Rave, 350 Hudson Street, 9th Floor, New York, New York, 10014). This system was designed and is developed and maintained by Medidata in a manner that is compliant with national and international Good Clinical Practice (GCP) data protection/data privacy and electronic record/electronic signature (e.g. 21 CFR Part 11) regulatory requirements.

Protocol Modifications

All protocol amendments must be issued by the Sponsor, signed and dated by the Investigator, and should not be implemented without prior IRB/EC approval, except where necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in Sponsor personnel, change of telephone number(s)). The Investigator will submit the protocol amendments to the IRB/EC as per their local requirements.

1.0 INTRODUCTION AND BACKGROUND

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer.[1] Surgical intervention is required in the treatment of lung cancer to remove localized tumors, as well as potentially affected lymph nodes, in order to prevent further spread of the disease. International guidelines for NSCLC treatment are closely linked to the cancer stage and the patient's general performance.[2] Surgery is most common in patients with Stage 0 NSCLC, but may also be performed in patients with Stage I or Stage II NSCLC, if tumors remain localized. Patients with Stage IIIA NSCLC could have resectable tumors or some form of metastases. Overall, the type of surgical procedure required varies depending on multiple factors, including the stage, location and cell types associated with the tumor. Limiting factors for surgery include poor overall performance status or an inadequate pulmonary reserve, as these patients will have a reduced chance of surviving the procedure. Surgical interventions are not appropriate for patients with a poor overall performance status as the risk of serious complications or peri-operative death may be too high. Surgical intervention decisions are made on the basis of the progression of the tumor as well as the general condition of the patient.

The surgical procedure performed under this protocol is Video-Assisted Thoracoscopic Surgery (VATS) lobectomy. VATS uses video technology to assist during thoracic surgical procedures. VATS is most commonly utilized in the treatment of lung cancer and can be used to extract cancerous tumors from the lungs through segmentectomy or lobectomy. A small video camera, for visualization of internal anatomy, is inserted into a patient's chest via an incision in the chest wall termed a port. Additional ports are created to allow the entry of surgical instruments. The pulmonary artery, pulmonary vein, and bronchus to the involved pulmonary lobe are individually dissected, ligated and divided. VATS is commonly utilized in the treatment of lung cancer.

Ethicon Endo-Surgery, Inc. has developed a powered vascular stapler, the ECHELON FLEX™ Powered Vascular Stapler with Advanced Placement Tip, which can transect pulmonary vessels in restricted narrow spaces near delicate vascular anatomy. With its narrow anvil and curved dissection tip, this stapler enhances visibility and provides precise placement.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of the study is to demonstrate that the frequency of hemostatic interventions/procedures required intra-operatively or post-operatively related to the transection of the pulmonary artery (PA) and pulmonary vein (PV) during VATS lobectomy with PVS is not increased when compared to standard of care (SOC).

3.0 INVESTIGATIONAL PLAN

3.1 GENERAL DESIGN

This prospective, randomized, controlled, multi-center study will collect and compare data from the surgeon's current SOC stapler (for PA/PV transection) and PVS. Approximately 200 individuals undergoing VATS lobectomy, and who meet study entry criteria, will be randomized in a 1:1 ratio to either the surgeon's current SOC stapler or PVS. Prospective subjects will be informed about the nature of the research, given the ICD to read, and if the subject understands the consent, will be asked to provide written consent (the ICD).

3.2 PRIMARY ENDPOINTS

The primary performance endpoint will be:

Incidence of hemostatic interventions/procedures completed for intra-operative bleeding related to the transection of the PA and PV during VATS lobectomy with the use of standard of care stapler (SOC) or powered vascular stapler (PVS) defined as:

- Hemostasis intervention: bleeding detected and controlled intra-operatively (additional stapling, over-sewing, clip placement, compression, use of suture, sealant, and/or buttress, and/or use of energy); or bleeding that occurs intra-operatively requiring blood or blood product transfusion or an additional surgical procedure (e.g. conversion to open).

No hemostasis intervention is defined as no bleeding at the staple line or bleeding that stops after initial blotting of staple line.

The primary safety endpoint will be:

Incidence of hemostatic interventions /procedures completed for post-operative bleeding related to the transection of the PA and PV during VATS lobectomy with the use of SOC or PVS:

- Hemostasis intervention: bleeding that occurs post-operatively requiring blood or blood product transfusion or an additional surgical procedure (related to PA and PV transection).

No hemostasis intervention is defined as no interventions needed for post-operative

bleeding (related to PA and PV transection).

3.3 ADDITIONAL MEASUREMENTS / DATA COLLECTED

a. Subject demographics;
b. Pain medication usage (two weeks prior to procedure through final study visit);
c. All adverse events;
d. Anticoagulants taken preoperatively (up to 30 days prior to Visit 2/Procedure) and concomitant medications associated with AEs and pain;
e. Relevant medical/surgical history (including hypertension and/or smoking history, if applicable);
f. Pain score assessments;
g. Procedure details;
h. Number of ports;
i. Overall operating room and procedure duration (including time to resection);
j. Use of other stapling devices for bronchus and parenchyma transection (number and color of cartridges);
k. Intra-operative and post-operative surgical interventions (not associated with transection of the PA/PV), if applicable;
l. Volume of estimated intra-operative blood loss;
m. Transfusion of blood or blood products;
n. Date(s) of chest tube removal;
o. Daily volume and characteristics of chest tube(s) drainage;
p. Device usability /articulation questions;
q. Surgeon assessment of visualization;
r. Surgeon Questionnaires;
s. American Shoulder and Elbow Surgeons (ASES) [3,4] Standardized Shoulder Assessment;
t. Concomitant procedures/interventions, if applicable; and
u. Length of stay (LOS) from admission through discharge.

The data collected for this study may be used for future research or enhancement of similar surgical tools.

4.0 INVESTIGATIONAL PLAN

4.1 OVERALL STUDY DESIGN

This is a prospective, randomized, controlled, multi-center study that is intended to demonstrate that the frequency of hemostatic interventions/procedures required intra-operatively or post-operatively related to the transection of the pulmonary artery (PA) and pulmonary vein (PV) during VATS lobectomy with PVS is not increased when compared to standard of care (SOC).

Eligible subjects will be randomized pre procedure in a 1:1 ratio to either the surgeon's current SOC stapler or PVS. Subjects will be followed post-operatively through discharge and at 4 weeks post-surgery (final visit can be conducted either by phone or office visit).

If the study surgeons have not completed previous ECHELON FLEX™ Powered Vascular Stapler with Advanced Placement Tip training, each surgeon must complete two procedures with ECHELON FLEX™ Powered Vascular Stapler with Advanced Placement Tip prior to their first randomized subject. These subjects will be considered part of a learning curve and will be analyzed separately from the randomized subjects.

4.2 RANDOMIZATION

In this non blinded study, randomization will be used to avoid bias in the assignment of the stapling device to be utilized for PA/PV transection for each subject, to increase the likelihood that attributes of the subject are evenly balanced between groups, and to enhance the validity of statistical comparisons between groups.

The Sponsor will assign the stapling device randomly to each subject on a 1:1 basis to either the surgeon's current SOC or PVS.

In the event that a potential subject fails inclusion/exclusion criteria prior to randomization, this subject will be considered a screen failure.

4.2.1 Inclusion Criteria

Subjects satisfying the following criteria will be eligible for participation in this study:

1. Subjects with a confirmed or suspected diagnosis of stage IA to stage IIIA non-small cell lung cancer scheduled for a lobectomy (Lung Cancer Staging per American Joint Committee on Cancer, 7th Edition[5]);
2. Subjects scheduled for VATS lobectomy in accordance with their institution's SOC;
3. Performance status 0-1 (Eastern Cooperative Oncology Group classification);
4. ASA score $\leq$ 3;
5. No prior history of VATS or open lung surgery (on the lung in which the procedure will be performed);
6. Willing to give consent and comply with study-related evaluation and treatment schedule; and
7. At least 18 years of age.

4.2.2 Exclusion Criteria

Subjects will be excluded from the study for any of the following:

1. Prior chemotherapy or radiation (within 30 days prior to the procedure or the duration of the subject's enrollment);

2. Pregnancy;
3. Physical or psychological condition which would impair study participation; or
4. The subject is judged unsuitable for study participation by the Investigator for any other reason.

All subjects signing consent who do not meet the inclusion/exclusion criteria and therefore do not proceed to Visit 2/Procedure, and are not randomized, will be recorded as screen failures. The relevant electronic Case Report Form (eCRF) pages will be completed for all screen failure subjects and the data will therefore be included in the study database.

4.3 PRIOR AND CONCOMITANT THERAPY

Study subjects may continue with their current medical care while in the study, including medications.

4.3.1 Concomitant Medications

Anticoagulants taken preoperatively (up to 30 days prior to Visit 2/Procedure) and peri-operative, intra-operative, and post-operative pain medication and/or medications prescribed due to an adverse event will be collected for this study. No other concomitant medications will be collected.

4.4 REMOVAL OF SUBJECTS FROM STUDY

A subject has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or the institution. Should a subject (or subject's legally authorized guardian/representative) decide to withdraw; all efforts will be made to collect and report the final visit observations as thoroughly and timely as possible.

Subjects who withdraw from the study prior to randomization will be considered screen failures and will be replaced. Subjects who withdraw from the study post-randomization will not be replaced. Subject participation may be terminated prior to completing the study for any of the reasons listed below. When a subject's participation is terminated prior to completing the study, the reason for withdrawal is to be documented on the Study Completion eCRF as well as in the source documentation:

Withdrawal of Consent:

The subject withdraws consent for participation in the study. Any method of contact with the subject in which they state they no longer want to participate in the study specific activities constitutes withdrawal of consent. When possible, the reason for withdrawal of consent will be documented.

Surgical:

The Investigator must withdraw a subject intra-operatively for the following reasons:

- Lobectomy not completed;

- Conversion to an open procedure, unless directly related to transection of the PA/PV (subject will be followed for safety up to 30 days post-op); or
- Use of robotic assistance during surgery.

Adverse Event:
When the subject experiences an adverse event and the Principal Investigator or Medical Director believes it is in their best interest to discontinue participation in the study, they will be withdrawn.

Death:
When possible, the cause of death will be documented.

Lost to follow-up:
When contact with the subject has been lost without completing a final visit assessment, and every attempt to contact has failed, the subject will be considered lost to follow-up. Final documentation regarding all attempts to contact the subject requesting their return for the final visit should be documented.

Site Termination or Study Termination:
A site or study may be terminated. When this occurs all subjects at the site will be withdrawn and documented as early termination. Reasons for site or study termination may include, but are not limited to the following:

- Administrative Concerns (e.g., inadequate subject enrollment, investigator/institution non-compliance, change of business strategy, etc.);
- Safety Issues, including those due to non-compliance, which substantially affect the risk to benefit ratio of the study subjects at a site or for the study as a whole; and
- Regulatory Body Mandate(s).

The Investigator has the right to terminate their participation at any time. Should this be necessary, procedures for termination will be provided by the Sponsor.

4.5 IDENTITY OF STUDY PRODUCT(S)

Product Code	Product Name	Manufacturer
PVE35A	ECHELON FLEX™ Powered Vascular Stapler with Advanced Placement Tip	Ethicon Endo-Surgery, LLC (Guaynabo, Puerto Rico, USA)
VASECR35	ENDOPATH ECHELON Vascular White Reload for Advanced Placement Tip	Ethicon Endo-Surgery, LLC (Guaynabo, Puerto Rico, USA)

The ECHELON FLEX™ Powered Vascular Stapler with Advanced Placement Tip is a sterile, single use instrument that simultaneously cuts and staples tissue. There are four staggered rows of staples, two on either side of the cut line. The ECHELON FLEX™ Powered Vascular Stapler with Advanced Placement Tip and reloads have a staple line that is approximately 35mm long and a cut line that is approximately 30 mm long. The shaft can rotate freely in both directions and an articulation mechanism enables the distal portion of the shaft to pivot to facilitate lateral access to the operative site.

Powered vascular stapler has been cleared for marketing by the FDA and is CE marked which allows for commercial distribution in the EU. The device will be used in accordance with product labeling and Instructions for Use (IFU).

4.6 PRODUCT ACCOUNTABILITY

The ECHELON FLEX™ Powered Vascular Stapler with Advanced Placement Tip and cartridges will be provided by the Sponsor and will be tracked using shipping invoices and device accountability logs. All product returns will be managed by contacting the Sponsor.

The powered vascular staplers must be kept in a secure area. Devices will only be used for treating subjects participating in the study, in accordance with the protocol. The study device inventory must be available for periodic inspection/verification.

4.7 STUDY PROCEDURES

4.7.1 PROCEDURE DESCRIPTION

VATS lobectomy will be performed according to the institution's SOC.

4.7.2 VISIT 1 – SCREENING (CAN OCCUR OVER SEVERAL DATES WITHIN 1-2 WEEKS OF VISIT 2- PROCEDURE)

Subjects will be evaluated according to the local investigator's preferred practice. Subjects will be selected for a surgical procedure based on the preoperative investigations and the local investigator's interpretation of the clinical picture.

Eligible subjects will be provided with the study information including the ICD.

The following screening activities will occur prior to the study procedure:

- The subject must be given ample time to review and sign the ICD;
- Collection of demographic information (year of birth, gender, ethnicity);
- Review and collection of relevant medical/surgical history, history of hypertension or smoking if applicable;
- Review/collection of inclusion/exclusion criteria and determination as to whether the subject is eligible for participation (retrospective data, per site SOC, is permitted to determine eligibility);
- ASES Standardized Shoulder Assessment;
- Anticoagulants taken preoperatively (up to 30 days prior to Visit 2/Procedure), including stop date; and
- Collection of current pain medications (within two weeks of the screening visit).

4.7.3 VISIT 2 –PROCEDURE

4.7.3.1.1 PRE-PROCEDURE

The following must be obtained prior to the surgical procedure:

- Date of hospital admission;
- Update to medical / surgical history, if applicable;
- Confirm inclusion and exclusion criteria;
- ASA score;
- Pain Medication updates, including preoperative pain medications; and
- Randomization

4.7.3.1.2 INTRA-OPERATIVE

Data collected during procedure:

- Overall Operating Room (OR) time;
- Duration of procedure (first incision to skin closure);
  - Includes time to completion of resection (capturing the time thoracoscopic camera is inserted until the specimen is received);
- Procedure data:
  - Location of affected lobe;
  - Number of pulmonary arteries (1, 2, or 3+);
  - Confirm visualization of the cut line indicator field prior to transection;
  - Confirm presence or absence of calcified hilar lymph nodes;
  - Use of other stapling devices for bronchus and

parenchyma transection (number and color of cartridges);
- Number of ports;
- Intra-operative surgical interventions (not associated with transection of the PA/PV), if applicable;
- Reason for conversion to open surgery, if applicable;
- Volume of estimated intra-operative blood loss;
- Transfusion products (and rationale for use), if applicable;
- Concomitant procedures/interventions performed, if applicable;
- Number of chest tubes placed and anatomic position;
- Tumor size and TNM staging, if available;

- Intra-operative interventions/procedures on PA/PV to stop bleeding, if applicable:
  - Hemostasis intervention: bleeding detected and controlled intra-operatively (additional stapling, over-sewing, clip placement, compression, use of suture, sealant, and/or buttress, and/or use of energy); or bleeding that occurs intra-operatively requiring blood or blood product transfusion or an additional surgical procedure (e.g. conversion to open).
- Device usage data:
  - Usability and articulation questions;
- Surgeon Device Questionnaire (***PVS procedures only***);
- Surgeon Satisfaction Questionnaire (***SOC and PVS procedures)***;
- SURG-TLX (***SOC and PVS procedures****);*
- Adverse Events;
- Pain medications given perioperative (i.e. spinal block, intercostal nerve blocks, etc.); and
- Concomitant medication (associated with AEs and pain)

4.7.4 Visit 3 – Post-operative through Discharge

Post procedure assessments will be completed from OR discharge until hospital discharge. Data to be collected includes:

- Post-operative interventions/procedures related to PA/PV bleeding, if applicable:
  - Hemostasis intervention: bleeding that occurs post-operatively requiring blood or blood product transfusion or an additional surgical procedure (and the relationship to SOC/PVS for PA/PV transection);

- Post-operative pain medications used;
- Date(s) of chest tube(s) removal;
- Daily volume and characteristics of chest tube(s) drainage;
- ASES Standardized Shoulder Assessment;
- Pain score assessment (incisional, trocar, and chest tube pain);
- Concomitant procedures/ interventions performed, if applicable;
- Adverse Events;
- Concomitant medication (associated with AEs and/or pain); and
- Discharge date

4.7.5 Visit 4- Final Visit (4 week follow up, post procedure)

This visit can be either an office visit or a telephone follow-up visit. Data to be collected includes:

- Post-operative interventions/procedures related to PA/PV bleeding, if applicable:
  - Hemostasis intervention: bleeding that occurs post-operatively requiring blood or blood product transfusion or an additional surgical procedure (and the relationship to SOC/PVS for PA/PV transection);
- Post-operative pain medications used;
- ASES Standardized Shoulder Assessment;
- Date(s) of chest tube(s) removal, if applicable;
- Daily volume and characteristics of chest tube(s) drainage, if applicable;
- Concomitant procedures/interventions performed, if applicable;
- Pain score assessment (incisional, trocar, and chest tube pain)
- Adverse Events;
- Concomitant medication (associated with AEs and pain); and
- Subject exited from the study

5.0 DATA MANAGEMENT AND INTEGRITY

5.1 DATA COMPLETION AND RECORD KEEPING

5.1.1 SOURCE DOCUMENTS

Source documents are documents on which information regarding subjects is first recorded, including printed, hand written, or electronic documents. Investigator subject files or hospital records generally are the basis of source document information. This includes but is not limited to, original subject files; hospital/clinic records; original recordings /tracing; digital images from automated instruments (e.g., cameras); radiographs; device accountability records; photographic negatives; and records kept at the investigation site, at the laboratories and at other departments involved in the clinical investigation.

Source documents must be retained by the Investigator as part of the subject's permanent medical record. The information in the source documents is used to

complete the eCRFs. All information captured on the eCRFs should be completely and accurately supported in source documentation. Any additional information relevant to the study should be included in the source documents. The Investigator will retain originals of all source documents, subject consent forms, and study data.

5.1.2 ELECTRONIC DATA CAPTURE

An electronic data capture (EDC) system will be utilized by study site personnel to transfer study data from source records (medical records and/or source document worksheets) onto common eCRFs. This system is a web-based, secure electronic software application (Medidata® Rave, Medidata® Rave, 350 Hudson Street, 9th Floor, New York, New York, 10014). This system was designed and is developed and maintained by Medidata in a manner that is compliant with national and international GCP data protection/data privacy and electronic record/electronic signature (e.g., 21 CFR Part 11) regulatory requirements. The EDC system will be used to facilitate the collection of all study data at the site. Designated site personnel will be responsible for entering subject data into the EDC system. All external and Sponsor internal users will be trained on the EDC application at a level dependent on their planned function. An EDC digital User Manual will be available under the help menu within the Medidata® Rave website to assist in the collection and entry of source data into the electronic casebook.

There is a 24/7/365 Help Desk Support line (and Email: helpdesk@mdsol.com) staffed by the outsourced vendor that will be available to respond to questions.

5.1.3 DATA COLLECTION

Each EDC eCRF will be completed by the PI or PI's designee. Every effort should be made to respond to all monitoring and/or data management questions on each eCRF as completion of the data is required by the protocol. A unique ID number will identify each subject. The subject's unique ID number will be visible on each eCRF. At no time should the subject name appear on the eCRFs.

All data should be recorded accurately and completely. The Investigator is responsible for reviewing and approving each completed eCRF. Assurance of overall review and approval will be documented by the Investigator electronically signing each subject's electronic casebook.

5.1.4 DATA CORRECTION

Required data corrections to eCRFs will be prompted via automated electronic edit checks and/or queries manually created by Sponsor reviewers. The change(s), individual making the change(s), and time the change(s) were made to the eCRFs will be automatically captured in the audit trail within Medidata® Rave.

5.1.5 DATA PRIVACY

The collection, use, and disclosure of all personal data, including subject health and medical information, are to be maintained in compliance with applicable personal data protection and security laws and regulations that govern protected health information and the informed consent given by each study subject. When collecting and processing such personal data, appropriate measures are to be taken to maintain the confidentiality of subject health and medical information and to prevent

access by unauthorized persons.

5.1.6 RECORD RETENTION, INSPECTION, AND CUSTODY

The PI must maintain all documentation related to the study until they receive Sponsor notification. The PI will allow representatives of the Sponsor, the FDA, or other applicable government regulatory agencies to inspect all study records, eCRFs, and corresponding portions of the subject's office and/or hospital medical records at regular intervals during the study. These inspections are to verify adherence to the protocol, integrity of the data being captured on the eCRFs, and compliance with applicable regulations.

Subject medical records will be maintained in a confidential manner. Study reports will not identify subjects by name. These reports may be submitted to the FDA and/or applicable regulatory authorities.

If custody of the records is transferred, notice of such a transfer should be given to the Sponsor no later than 10 working days after the transfer occurs.

5.2 MEDICAL DICTIONARY CODING

Medical dictionary coding of verbatim AE and SAEs captured on eCRFs will be performed using a coding thesaurus algorithm. The Medical Dictionary for Regulatory Activities and World Health Organization Drug Dictionary will be used after data entry and query resolution, via auto-encoding and interactive coding processes.

6.0 DATA QUALITY ASSURANCE

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel prior to the study, and periodic monitoring visits by the Sponsor. The Sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits or periodic reviews of the EDC system; any discrepancies will be resolved with the Investigator or designees, as appropriate. The data entered into the clinical study database will be verified for accuracy.

6.1 INVESTIGATOR TRAINING

Prior to screening subjects for this study, the PI, sub-investigators, study coordinators, and other designated staff (as applicable) will be provided information on study execution, data collection, and procedures specific to this clinical protocol.

6.2 MONITORING

This study will be monitored by the Sponsor to ensure:

- The rights and well-being of the subjects are protected;
- Reported study data is accurate, complete, and verifiable from source documents; and
- The conduct of the study is in compliance with the currently approved protocol/amendment(s), applicable GCPs, and with applicable local/regional regulatory requirements.

The extent and nature of monitoring will be predetermined and based on considerations such as the objective, design, complexity, and endpoints of the study and mutually agreed to by the Sponsor and investigators. Monitors will comply with established written standard operating procedures as well as procedures (i.e.,

monitoring plan) specified by the Sponsor for monitoring this study. These monitoring procedures are characterized in the monitoring plan for this study.

6.3 PROTOCOL DEVIATIONS

A deviation (any activity conducted outside the parameters established by the study protocol) can be identified from a number of sources. Potential sources include, but are not limited to: a member of the Investigator's staff, a Sponsor representative during monitoring visits, or a member of the data management or statistical groups when entering or analyzing data. Regardless of the source, it is crucial to document the deviation. The PI will report protocol deviations to the IRB/EC as required by the IRB/EC procedures. All deviations will be captured in the source as well as the eCRF.

7.0 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL AND ANALYTICAL PLANS

The Sposor's Data Management and Biostatistics groups will be responsible for the analysis of data from this protocol. A comprehensive and detailed Statistical Analysis Plan (SAP) will be finalized prior to database lock and will supplement the statistical design and analysis described in this section.

Categorical variables will be summarized descriptively by frequencies and associated percentages. Continuous variables will be summarized descriptively by number of subjects, mean, standard deviation, median, minimum, and maximum.

7.2 DETERMINATION OF SAMPLE SIZE

Approximately 200 subjects will be randomized in the study in a 1:1 ratio to standard of care or powered vascular stapler. Historical clinical study data on a similar powered surgical stapler demonstrated a need for staple line interventions in approximately 6% of firings on the pulmonary artery or pulmonary vein. This data also showed an average of 2.6 to 2.9 firings per subject, and it is expected, given differences in device design, that each subject will require 3 to 4 firings on the pulmonary vein or pulmonary artery in the current study with powered vascular stapler.

Given that it is expected to have a minimum of 260 firings in each group, the sample size of approximately 200 subjects is considered adequate for descriptive summarization of the primary performance endpoint, i.e. number and frequency of intra-operative surgical interventions. Assuming an approximate background intervention rate of 6%, the given sample size will provide reasonable precision in the estimation of the intervention rate to an expected margin of error for a 95% confidence interval of at most 2.9% for each group.

7.3 ANALYSIS SETS

There will be three analysis sets defined:

- The Full Analysis Set (FAS) will consist of all randomized subjects who had the procedure performed and provide data on number of surgical interventions;
- The Per Protocol (PP) Analysis Set will consist of all subjects in the FAS who had no major protocol violations;
- The Safety Set consists of all randomized subjects on whom the procedure is started.

The primary performance endpoint analysis will be performed on the Full Analysis Set and subjects will be classified according to their randomized treatment group. The primary performance endpoint analysis will also be performed on the PP set as a sensitivity analysis to the results on the FAS. The summary of additional endpoints will also be performed on the Full Analysis Set. Analysis of the primary safety endpoint and adverse events summaries will be performed on the Safety Set.

7.4 ANALYSIS OF EFFECTIVENESS

Summary statistics and 95% confidence intervals will be provided for the number and frequency of interventions for the set of SOC subjects and PVS subjects separately. This will be performed based on the total number of firings. An intervention is defined as any firing which is classified as hemostasis intervention. To establish that the intervention rate is not increased compared to SOC, a 95% confidence interval for the difference in proportion of firings requiring interventions for PVS minus SOC will be calculated and powered vascular stapler will be considered to have acceptable performance if the upper bound of the 95% confidence interval does not exceed 3%.

Additional endpoints will be summarized with descriptive statistics and 95% confidence intervals as appropriate for continuous or categorical measurements.

7.5 STATISTICAL/ANALYTICAL ISSUES

7.5.1 HANDLING OF DROPOUTS OR MISSING DATA

All summaries will be performed only on subjects undergoing the surgical procedure and only observed data will be summarized. There will be no imputation of data for early terminated subjects or for missing data within the database.

7.5.2 INTERIM ANALYSES AND DATA MONITORING

No interim analysis is planned for this study.

7.5.3 MULTICENTER STUDIES

No adjustment for center is planned in the statistical analysis. Center specific analyses may be conducted pending within-center sample size to understand the effect that surgeon techniques and site standard of care may have on the overall results.

7.5.4 MULTIPLE COMPARISONS/MULTIPLICITY

No adjustment for multiplicity is necessary since multiple hypotheses are not being tested.

7.6 ANALYSIS OF SAFETY

The number and percentage of subjects requiring hemostasis interventions post-operatively that are classified as related to SOC/PVS for PA/PV transection (e.g. need for blood product transfusion or additional surgical procedure) will be summarized for each group as a primary safety endpoint.

Safety will be assessed through the incidence of AEs and serious adverse events (SAEs), which will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs will be summarized at the MedDRA system organ class and preferred term level. Incidence of AEs will also be summarized by maximum severity. All reported adverse events will be listed.

8.0 RISKS AND BENEFITS OF THE STUDY DEVICE AND CLINICAL INVESTIGATION

The procedure being performed with powered vascular stapler is identical to the procedure subjects would receive as part of their standard of care procedure. To date, no risks have been reported beyond standard risks associated with VATS lobectomy. This study may or may not provide any benefits to the subject.

9.0 ADVERSE EVENTS AND PRODUCT COMPLAINTS

9.1 DEFINITIONS

9.1.1 ADVERSE EVENT

An adverse event is defined as any undesirable clinical occurrence in a subject that may or may not be attributable to the device or procedure. All AEs, regardless of their relationship to the procedure or device, are to be recorded in the eCRF and reported to the Sponsor.

In addition, the Investigator is required to provide:

- The onset and resolution dates of the event;
- The severity of the event;
- The outcome of the event;
- The relationship of the event to procedure and/or device (ECHELON FLEX™ Powered Vascular Stapler with Advanced Placement Tip or standard of care stapler); and
- The action taken for the medical management of the event.

Post-operative pain is expected and will not be documented as an adverse event unless the Investigator considers the pain to exceed what is typically anticipated following a VATS procedure. (This data is separate from incisional, trocar, and / or chest tube pain).

9.1.2 ANTICIPATED ADVERSE EVENTS

An expected morbidity/procedural complication is defined as an AE that is known to be common or usual in nature, severity, or incidence during VATS lobectomy in subjects with confirmed or suspected diagnosis of stage IA to stage IIIA non-small

cell lung cancer.

A list of anticipated AEs that may occur during this study are listed in Appendix I.

9.1.3 SERIOUS ADVERSE EVENT

It is the Investigator's responsibility to determine if an AE is an SAE.

SAEs are AEs that:

- Led to death,
- Led to serious deterioration in the health of the subject, that either resulted in
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
    - Led to fetal distress, fetal death or a congenital abnormality or birth defect

Note: "Death" should not be reported as an adverse event. The cause of death should be reported as an adverse event. The only exception is "Sudden Death" when the cause is unknown.

9.1.4 SEVERITY OF ADVERSE EVENTS

It is the Investigator's responsibility to assess the severity of an AE. A change in severity may constitute a new reportable AE.

The following guideline should be used to determine the severity of each adverse event:

- **MILD:** Awareness of experience, but easily tolerated. No medical intervention required.
- **MODERATE:** Enough discomfort to interfere with usual activities. Medical intervention required.
- **SEVERE**: Inability to carry out usual activities. Medical intervention (including hospitalization or prolongation of hospitalization) required.

9.1.5 RELATIONSHIP OF ADVERSE EVENTS

It is the Investigator's responsibility to assess the relationship of an AE to the study procedure (VATS lobectomy) and powered vascular stapler or SOC.

The following guidelines should be used in determining the relationship of an adverse event to the study device, study procedure, or other causality:

- **Not Related** – A clinical event (including abnormal laboratory result) that results from causes extraneous to administration of device/procedure/other and is most likely due to alternative etiology, (i.e., pre-existing condition, underlying disease, intercurrent illness, concomitant medications);
- **Possibly** – A clinical event (including abnormal laboratory result) that presents

an unlikely association between device/procedure/other, which cannot be ruled out with certainty, but could also be explained by alternative etiology;

- **Related**– A clinical event (including abnormal laboratory result) that presents a strong temporal relationship between device/procedure/other, in which an alternative etiology is unlikely; or
- **Unknown** – A clinical event (including abnormal laboratory result) that cannot be determined to be related or unrelated to device/procedure/other given the information obtained.

9.1.6 Product Complaints

A product complaint is defined as any written, electronic or oral communication that alleges deficiencies related to the identity, labeling, quality, durability, reliability, safety, effectiveness, or performance of a device (i.e., stapler) after it is released for distribution (policy of Johnson and Johnson Medical Device Quality management). A product complaint may or may not be associated with an AE/SAE.

9.2 REPORTING PROCEDURES FOR ADVERSE EVENTS/PRODUCT COMPLAINTS

9.2.1 REPORTING ADVERSE EVENTS

Data related to AEs will be recorded in the source documentation from the time of study enrollment (first incision) until the subject completes the study or terminates early. All AEs that are unresolved at study completion (or early termination) will be recorded as ongoing at study end.

Data related to SAEs will be collected until event resolution, or until the event is considered stable, or until all attempts to determine the resolution of the event are exhausted.

9.2.2 Reporting Serious Adverse Events

The site must complete the SAE eCRF within 24 hours of becoming aware of the event.

Supporting SAE documentation can be faxed to:

US sites:
Fax: 1-513-337-1392
Study Number: ESC-15-001

EU sites:
Fax: + 44-1506-5946-91
Study Number: ESC-15-001

The Investigator will also be required to assess if the SAE is considered anticipated (see Appendix I) and if the event involved a product complaint. The report of an SAE by a study site does not constitute an admission that study personnel or the user facility (hospital/clinic) caused or contributed to the event.

The study site is also responsible for submitting to the reviewing IRB/EC according to their IRB/EC procedures.

9.2.3 Reporting Product Complaints

All product complaints related to powered vascular stapler shall be documented throughout the clinical investigation.
Product complaints related to powered vascular stapler must be reported to the Sponsor in a timely manner and no later than 24 hours after becoming aware of the event. The Product Complaint Form must be emailed to the EES Customer Complaint team at the following email address:

Productcomplaint1@its.jnj.com

One copy of the processed form should be kept on-site and the device should be retained. EES representatives will organize collection of the device for evaluation as needed.

10.0 REFERENCE LIST

1. National Cancer Institute
2. Diagnosis and Management of Lung Cancer: ACCP Guidelines (2007)
3. Michener, L. (2002). J Shoulder Elbow Surg;11:587-94
4. Wilson W. (2003). European Journal of Cardio-thoracic Surgery; 23:390–396
5. American Joint Committee on Cancer, Lung Cancer Staging 7th edition

11.0 APPENDIX I: ANTICIPATED ADVERSE EVENTS

Associated with Surgery and General Anesthesia	Thoracic Surgery Specific
Acute Lung Injury	Air/Gas Embolism
Acute Respiratory Distress Syndrome	Angina
Adhesions	Broncho pleural fistula
Altered Mental Status	Chylothorax
Anaphylaxis	Diaphragmatic Injury
Anemia	Empyema
Angina	Esophageal Injury
Atelectasis	Hemothorax
Bacteremia	Hernia
Bleeding	Intercostal nerve injury
Bradycardia	Pneumothorax
Cardiac Arrhythmia	Prolonged Air Leak
Central line infection	Thoracic duct injury
Cerebrovascular Accident / Stroke	Thromboembolic Event
Congestive Heart Failure	Wound infection
Constipation	Tightness of the chest
Death	
Deep Venous Thrombosis	
Dehydration	
Dementia	
Diarrhea	
DIC, Coagulopathy	
Dizziness	
Electrolyte Imbalance	
Fever, Pyrexia	
Headache	
Hematuria	
Hypertension	
Hypotension, shock	
Hypoxia	
Ileus	
Infection/SSI/Abscess	
Jaundice	
Lethargy	
Leukocytosis	
Liver Failure	

Mesenteric Infarct	
Mesenteric Ischemia	
Myocardial Infarction	
Nausea	
Obtundation, Depressed Level of Consciousness	
Oliguria	
Pain (increased/severe/chronic)	
Pneumonia	
Pulmonary Embolism	
Renal Failure	
Respiratory Failure	
Respiratory Insufficiency	
Sepsis	
Somnolence	
Systemic Inflammatory Response Syndrome	
Tachycardia	
Thrombocytopenia	
Thromboembolic Event	
Thrombosis	
TIA	
Tightness of the chest, Angina	
Tinnitus	
Urinary Retention	
Urinary Tract Infection (UTI)	
Volume Depletion, Hypovolemia	
Vomiting	
Wheezing	
Wound Dehiscence	