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A Prospective, Single-Arm, Multi-Center Study of the ECHELON ENDOPATH™ Staple Line Reinforcement Device in Gastric and Lung Resection Procedures

Trial Number: ESC_2018_03

Document	Effective Date
Original	5 SEP 2019
Amendment 1	1 APR 2020
Amendment 2	27 JAN 2021
Amendment 3 – Gastric procedures only	11 JUN 2021

Sponsor:
Ethicon Endo-Surgery, Inc.
4545 Creek Road
Cincinnati, Ohio 45242

Anticipated Regulatory Classifications:
Class II in the United States

Name of Finished Product:
ECHELON ENDOPATH™ Staple Line Reinforcement

This is a sterile, bioabsorbable staple line reinforcement device intended for use in surgical procedures in which soft tissue transection or resection with staple line reinforcement is desired.

Sponsor's Medical Monitor:
[redacted]
Senior Medical Director for Endomechanical and Energy
4545 Creek Rd.
Cincinnati, OH 45242

This study will be performed in compliance with Good Clinical Practice (GCP) and in accordance with the Declaration of Helsinki, as well as any other applicable local and country regulatory requirements.

PROTOCOL SIGNATURE PAGE

A Prospective, Single-Arm, Multi-Center Study of the ECHELON ENDOPATH™ Staple Line Reinforcement Device in Gastric and Lung Resection Procedures

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Approvals:

[redacted]

Franchise Clinical Head — Date

Ethicon Endo-Surgery, Inc.

This study will be performed in compliance with GCP and in accordance with the Declaration of Helsinki, as well as any other applicable local and country regulatory requirements.

INVESTIGATOR SIGNATURE PAGE

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 (SAEs) as soon as possible, but no later than 72 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;
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting the above commitments; and
- Provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the conduct of the study.

I will ensure that the Institutional Review Board (IRB) 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 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 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.

_____ _____

Signature of Principal Investigator (PI) Date

_____

Printed Name of PI

CLINICAL TRIAL PROTOCOL SYNOPSIS

Anticipated Regulatory Classifications:	Class II in United States
Indication:	ECHELON ENDOPATH Staple Line Reinforcement is indicated for use in surgical procedures in which soft tissue transection or resection with staple line reinforcement is needed. ECHELON ENDOPATH Staple Line Reinforcement can be used for reinforcement of staple lines during lung resection and bariatric surgical procedures. The device can also be used for reinforcement of staple lines during gastric, small bowel and colorectal procedures.
Objective(s):	The primary objective of this study is to evaluate safety following use of ECHELON ENDOPATH Staple Line Reinforcement (ECHELON SLR) in subjects undergoing indicated gastric and lung resection procedures. The secondary objective will be to capture usability data of the device.
Overview of Study Design:	This prospective, single-arm, multi-center study will collect clinical data in a post-market setting by procedure group (gastric and lung resection). Investigators will perform each procedure using the device in compliance with their standard surgical approach and the ECHELON SLR instructions for use (IFU). Subjects will be consented and screened anytime during a period of 8 weeks prior to the date of surgery. Subjects will be considered treated when at least one ECHELON SLR has been placed during the procedure. All treated subjects will be followed post-operatively through discharge and again at 28, 70, and 135 days (± 14 days) post-surgery; therefore, from the surgery date to study exit, the duration will be approximately 19 weeks.

Number of Subjects:	A minimum of 243 treated subjects (maximum of 431 treated subjects) will be included in the study from up to 16 sites in the United States with the following procedure targets: • A minimum of 112 treated subjects for gastric procedures; and • A minimum of 131 treated subjects for lung resection procedures. Given the lack of available clinical data on the ECHELON SLR, an adaptive approach to sample size re-estimation will occur after approximately 50% of the originally planned sample size in each group has been enrolled. The purpose of this interim analysis will be to estimate the rate of the primary endpoint in each procedure group as well as to understand the size of the relative reduction in the rate of the primary endpoint in relation to published literature. Based on these observed values, the sample size will be re-estimated. Upon completion of the sample size re-estimation, the Sponsor will determine if enrollment will continue to the originally planned enrollment values above (the minimum number listed above for each procedure group), stop at the time of the interim analysis due to futility, or increase the sample size in one or both groups if the true endpoint rate or effect size differ from the original estimates.
Criteria for Inclusion:	Subjects satisfying the following criteria will be considered eligible for enrollment in this study: 1. Primary procedure (gastric or lung resection) where the ECHELON SLR is planned to be used for reinforcement of staple lines per the IFU in either a or b: a. Gastric procedures limited to laparoscopic gastric resection, robotic laparoscopic gastric resection, partial gastrectomy, gastric wedge resection, subtotal gastrectomy, laparoscopic Roux-en-Y gastric bypass, and robotic laparoscopic gastric bypass; or b. Lung resection procedures that include lobectomy, segmentectomy or wedge resection, and lung volume reduction surgery, and may be video assisted thoracic surgery (VATS) or open procedures; 2. Willingness to give consent and comply with all study-related evaluations and visit schedule; and 3. At least 18 years of age.
Criteria for Exclusion:	Subjects meeting any of the following criteria will be considered ineligible for enrollment in this study: <u>Preoperative</u> 1. Physical or psychological condition which would impair study participation; 2. Gastric procedures: Body mass index (BMI) ≥ 50.0 kg/m^2, or lung resection procedures: BMI ≥ 46.0 kg/m^2;

	3. The procedure is a revision/reoperation for the same indication or same anatomical location; 4. A procedure where extended wound or organ support is required; 5. Any medical condition that the investigator deems could impact inflammatory or immune response; 6. Concurrent treatment with medications that the investigator deems could have influence on wound healing; 7. History of hypersensitivity to polyglactin (Vicryl®), Polydioxanone (PDO or PDS), or hypersensitivity to related products (cross-allergy); or 8. Enrollment in a concurrent interventional clinical study that could impact the study endpoints. <u>Intraoperative</u> 1. Per surgeon discretion, presence of adhesions that could lead to an increased risk of leak occurrence at a different location than the staple line. 2. Per surgeon discretion, medical finding intraoperatively such that the procedural plan is changed and ECHELON SLR is not used during the procedure.
Test Product(s):	ECHELON SLR: Product Code | Description | Reinforcement Length ECH60R | ECHELON ENDOPATH™ Staple Line Reinforcement | 60mm
Reference Therapy/Product:	No comparator product is being used in this study.
Duration of Treatment:	Subjects will be exposed to the study device during the procedure and will be followed for approximately 135 days. The device will be used as indicated in the IFU. The ECHELON SLR is composed of materials that are essentially absorbed within 120 days.
Criteria for Evaluation:	Primary endpoint: • Incidence of device-related adverse events (AEs) through the 70-day post-procedure follow-up visit. Specific device-related AEs that will be captured and counted toward the primary endpoint are listed below. ○ Gastric ▪ Bleeding (defined as below) • Occurrence of post-operative blood transfusion deemed related to bleeding at the staple line; or

	• Return to operating room before 70-day post-procedure follow-up visit due to bleeding deemed related to the staple line; ▪ Leak (defined as below) • Occurrence of intra-operative or post-operative gastrointestinal leak related to the staple line as documented intra-operatively, by clinical exam, or radiographically; ▪ Stricture (defined as below) • Occurrence of stricture documented radiographically or by endoscopy along the staple line; ○ Lung Resection ▪ Prolonged air leak deemed related to the staple line (defined as below) • Greater than postoperative day 7 (procedure=day 0); ▪ Empyema (defined as below) • Purulent fluid collection in the pleural space documented radiographically, excluding chronic empyema Secondary performance endpoints: • Number of study devices replaced during surgery due to slipping or bunching or not properly loaded onto stapler cartridge; and • Device questionnaire by procedure group (gastric and lung resection) to capture usability.
Statistical Analysis:	**<u>Analysis Sets</u>** The summary of all performance and safety endpoints will be performed on the set of subjects in whom the ECHELON SLR is utilized during the surgical procedure. The summary of all primary and secondary endpoints will be performed by procedure group (gastric or lung resection). **<u>Primary Endpoint Analyses</u>** The following hypotheses will be evaluated for the primary endpoint for gastric procedures: $H_0: p_G \geq 14.0\%$ $H_1: p_G < 14.0\%$ Where p_G is the percentage of subjects experiencing at least one occurrence of bleeding, leak, or stricture through 70 days. A 95% confidence interval will be calculated for p based on the sample proportion of subjects experiencing the endpoint using the Normal approximation to the Binomial distribution, and the upper limit of this confidence interval will be compared to 14.0% to evaluate the above hypotheses. A p-value will be determined based on the same Normal

	approximation methodology. A similar methodology will be applied to the data observed in lung procedures to evaluate the following hypotheses: $H_0: p_L \geq 12.0\%$ $H_1: p_L < 12.0\%$ Where p_L is the percentage of subjects experiencing at least one occurrence of prolonged air leak or empyema through 70 days. **Secondary Endpoint and Safety Analyses** Summary statistics will be provided by procedure group for all procedure-related variables measured in this study including number of study device(s) replaced during surgery due to slipping or bunching and device questionnaires to capture usability. Counts and percentages will be provided for number of staple line reinforcement devices used during the procedure. All device- and procedure-related AEs reported during the study will be coded to the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be assessed for seriousness, severity, action taken, and outcome. Adverse events will be summarized by MedDRA system organ class and preferred term by procedure group and in total. Serious AEs will be summarized in a similar manner.

TABLE OF CONTENTS

Page

PROTOCOL-SPECIFIC ACRONYMS AND ABBREVIATIONS

Acronyms/Abbreviations	Terms
ADE	Adverse device effect
AE	Adverse event
ASA	American Society of Anesthesiologists
BMI	Body mass index
CFR	Code of Federal Regulations
C-SATS	Crowd-sourced assessment of technical skills
ECHELON SLR	ECHELON ENDOPATH™ Staple Line Reinforcement
eCRF	Electronic case report form
EDC	Electronic Data Capture
EES	Ethicon Endo-Surgery, Inc.
FDA	Food and Drug Administration
GCP	Good clinical practice
ICD	Informed consent document
IFU	Instructions for use
IRB	Institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	Standard of care
USADE	Unanticipated serious adverse device effect
VATS	Video-assisted thoracic surgery

ETHICS

Institutional Review Board

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) that complies with governmental requirements. The approving IRB will be responsible for the initial and continuing review and approval of this clinical study. Participating investigators will be required to promptly report to the IRB as required by the IRB's policies. Additionally, investigators will be required to refrain from making any changes in the clinical investigation plan without Sponsor and IRB 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 GCP and in accordance with the Declaration of Helsinki, 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 study. An IRB 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 approval before implementation. Each subject will be required to sign any amended ICD (as required by the IRB) 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 up to sixteen surgery centers in the United States under a single protocol approved by each participating site's IRB 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 the Sponsor 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 GCP data protection/data privacy and electronic record/electronic signature (e.g. 21 Code of Federal Regulations [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 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 medical monitor(s), change of telephone number(s)). The Investigator reports the protocol amendments to the IRB as per their local requirements.

1.0 INTRODUCTION

Staple line complications are an important issue to consider in gastric and lung resection surgical procedures. Various types of staple line reinforcement devices currently exist and are used for reinforcing staple lines including fibrin glue and other sealants, suture oversewing, and buttressing. For buttressing, some of the most commonly used reinforcement buttressing materials include bovine pericardium and biocompatible glycolide copolymer.

The Sponsor, EES, has developed the ECHELON ENDOPATH Staple Line Reinforcement (ECHELON SLR) for use in surgical procedures in which soft tissue transection or resection with staple line reinforcement is needed. ECHELON ENDOPATH Staple Line Reinforcement can be used for reinforcement of staple lines during lung resection and bariatric surgical procedures. The device can also be used for reinforcement of staple lines during gastric, small bowel and colorectal procedures.

2.0 STUDY OBJECTIVES

The primary objective of this post-market study is to evaluate safety following use of the ECHELON SLR in subjects undergoing indicated gastric and lung resection procedures. The secondary objective will be to capture usability data of the device.

2.1 PRIMARY ENDPOINT

The primary endpoint for this study is the incidence of device-related AEs through the 70-day post-procedure follow-up visit. Specific device-related AEs that will be captured and counted toward the primary endpoint are listed below.

- Gastric
  - Bleeding (defined as below)
    - Occurrence of post-operative blood transfusion deemed related to bleeding at the staple line; or
    - Return to operating room before 70-day post-procedure follow-up visit due to bleeding deemed related to the staple line;
  - Leak (defined as below)
    - Occurrence of intra-operative or post-operative gastrointestinal leak related to the staple line as documented intra-operatively, by clinical exam, or radiographically;
  - Stricture (defined as below)
    - Occurrence of stricture documented radiographically or by endoscopy along the staple line;
- Lung Resection
  - Prolonged air leak deemed related to the staple line (defined as below)
    - Greater than postoperative day 7 (procedure=day 0);
  - Empyema (defined as below)
    - Purulent fluid collection in the pleural space documented radiographically, excluding chronic empyema

2.2 SECONDARY PERFORMANCE ENDPOINTS

The secondary performance endpoints for this study are listed below.

- Number of study devices replaced during surgery due to slipping or bunching or not properly loaded onto stapler cartridge; and

- Device questionnaire by procedure group (gastric and lung resection) to capture usability.

2.3 ADDITIONAL KEY DATA COLLECTED

Additional key data collected for evaluation in this study are:

- Endocutter and reload used (type, name, and color [for reload]) for each firing during the procedure along with which firings are associated with the study device;
- Total number of study devices used during the procedure;
- If intervention used for intra-operative bleeding on the staple line, capture type and number of interventions used;
- Occurrence of blood transfusion (record the total required units of blood, rationale, and if related to staple line);
- Date(s) of chest tube placement and removal, daily volume and characteristics of chest tube drainage;
- Air leak duration in lung resection procedures;
- Surgical procedure conducted (and technique used);
- Procedure duration;
- Hospital stay duration; and
- Readmission for procedural-related complications.

3.0 INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN - DESCRIPTION

This prospective, single-arm, multi-center study will collect clinical data in a post-market setting by procedure group (gastric and lung resection). Investigators will perform each procedure using the device in compliance with their standard surgical approach and the ECHELON SLR IFU.

Subjects will be consented and screened anytime during a period of 8 weeks prior to the date of surgery. Subjects will be considered treated when at least one ECHELON SLR has been placed during the procedure. All treated subjects will be followed post-operatively through discharge and again at 28, 70, and 135 days (± 14 days) post-surgery; therefore, from the surgery date to study exit, the duration will be approximately 19 weeks.

3.2 STUDY POPULATION

3.2.1 Enrollment

Subjects will be recruited from the PI's existing patient population who plan to have an elective gastric or lung resection surgical procedure. Eligible subjects will be consecutively approached for participation so as to remove the potential of subject selection bias. Subjects will be considered enrolled at the time of consent signing. Subjects will be considered treated when at least one ECHELON SLR has been placed during the procedure. Gastric procedures are limited to laparoscopic gastric resection, robotic laparoscopic gastric resection, partial gastrectomy, gastric wedge resection, subtotal gastrectomy, laparoscopic Roux-en-Y gastric bypass, and robotic laparoscopic gastric bypass. Lung resection procedures include lobectomy, segmentectomy or wedge

resection and lung volume reduction surgery, and may be VATS or open procedures. Up to 16 centers in the United States will be selected as study sites. Each participating investigator is expected to perform a minimum of five gastric or lung resection procedures using the ECHELON SLR. A minimum of 243 treated subjects (maximum of 431 treated subjects) are planned to be in the study with a minimum of 112 treated subjects for gastric procedures and a minimum of 131 treated subjects for lung resection procedures.

3.2.2 Inclusion Criteria

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

1. Primary procedure (gastric or lung resection) where ECHELON SLR is planned to be used for reinforcement of staple lines per the IFU in either a. or b.:
    a. Gastric procedures limited to laparoscopic gastric resection, robotic laparoscopic gastric resection, partial gastrectomy, gastric wedge resection, subtotal gastrectomy, laparoscopic Roux-en-Y gastric bypass, and robotic laparoscopic gastric bypass; or
    b. Lung resection procedures that include lobectomy, segmentectomy or wedge resection, and lung volume reduction surgery, and may be VATS or open procedures;
2. Willingness to give consent and comply with all study-related evaluations and visit schedule; and
3. At least 18 years of age.

3.2.3 Exclusion Criteria

Subjects meeting any of the following criteria will be considered not eligible for enrollment in this study:

<u>Preoperative</u>

1. Physical or psychological condition which would impair study participation;
2. Gastric procedures: Body mass index (BMI) ≥ 50.0 kg/m^2, or lung resection procedures: BMI ≥ 46.0 kg/m^2;
3. The procedure is a revision/reoperation for the same indication or same anatomical location;
4. A procedure where extended wound or organ support is required;
5. Any medical condition that the investigator deems could impact inflammatory or immune response;
6. Concurrent treatment with medications that the investigator deems could have influence on wound healing;
7. History of hypersensitivity to polyglactin (Vicryl®), Polydioxanone (PDO or PDS), or hypersensitivity to related products (cross-allergy); or
8. Enrollment in a concurrent interventional clinical study that could impact the study endpoints.

Intraoperative

1. Per surgeon discretion, presence of adhesions that could lead to an increased risk of leak occurrence at a different location than the staple line.
2. Per surgeon discretion, medical finding intraoperatively such that the procedural plan is changed and ECHELON SLR is not used during the procedure.

3.2.4 Screening Failures

All subjects signing consent who do not have at least one ECHELON SLR placed during their procedures will be recorded as screen failures. For subjects who are determined to be screen failures, only the relevant eCRF pages (inclusion/exclusion criteria, demographics, AEs, subject completion/discontinuation) will be completed.

3.2.5 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, 1) all data collected up to the point of withdrawal will be considered for analysis; and 2) all efforts will be made to collect and report the final visit observations as thoroughly and timely as possible. Participation may be terminated prior to completing the study for any of the reasons listed below (reasons that do not fit the categories below will be documented as "other").

Adverse Event

When the subject experiences an AE and the Investigator or Medical Monitor believes it is in the best interest of the subject to discontinue participation in the study, the subject will be withdrawn from the study.

Lost to follow-up

When contact with the subject has been lost without completing a final contact assessment, and every attempt to contact the subject has failed, the subject will be considered lost to follow-up. All attempts to contact the subject requesting his/her return for the final visit must be documented.

Withdrawal of consent

Any method of contact with the subject (or subject's legally authorized guardian/representative) in which he/she state they no longer want to participate in the study specific activities constitutes withdrawal of consent for participation in the study. When possible, the reason for withdrawal of consent will be documented.

Site Termination or Study Termination

A study site or the entire study may be terminated. When this occurs, all subjects currently enrolled at the site will be withdrawn and documented as early terminations. 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, or those that substantially affect the risk to benefit ratio of the study subjects at a site or for the study as a whole; or
- Regulatory Body Mandate(s).

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

Death

- When possible, the cause of death will be documented.

Other (which may include)

- Investigator recommendation.

3.2.6 Subject Replacement in Study

Treated subjects who withdraw or are terminated early from the study will not be replaced.

3.3 STUDY PROCEDURES

3.3.1 Procedure Description

Elective gastric and lung resection procedures where ECHELON SLR is indicated for use (See Section 3.2.1 for the study specific procedures) will be performed per the institution's standard of care (SOC).

3.3.2 Identity of Study Products

The ECHELON SLR is the study product for this study. Per the ECHELON SLR IFU, it should only be used with ECHELON ENDOPATH GST 60 mm reload cartridges.

For this study, only the ECHELON FLEX™ Powered Plus Stapler (with ECHELON ENDOPATH GST 60 mm cartridges) should be used with the ECHELON SLR.

3.3.2.1 Device Description

The ECHELON SLR (Figure 1) is a sterile, bioabsorbable staple line reinforcement. The applicator contains a set of reinforcement materials: one each for the upper and lower stapler jaws.

Figure 1: Image of the ECHELON SLR.

The reinforcement material is composed of a VICRYL® material coated with a thin polydioxanone film on each side. The VICRYL component is prepared from polyglactin 910, a synthetic absorbable copolymer of glycolide and lactide, derived respectively from glycolic acid and lactic acids. The polyglactin 910 component is essentially absorbed

within 120 days. The VICRYL material is degraded via a combination of hydrolytic and enzymatic pathways and has been found to be both biocompatible and nonantigenic, with a history of use as bioabsorbable sutures, membranes and other implantable devices.

The polydioxanone which coats the VICRYL is a poly (p-dioxanone) polymer. The polydioxanone is essentially absorbed within 120 days. The reinforcement material elicits a mild tissue reaction during absorption. The polydioxanone material is degraded via a combination of hydrolytic and enzymatic pathways and has been found to be both biocompatible and nonantigenic, with a history of use as bioabsorbable sutures.

The ECHELON SLR contains a pre-applied, patterned adhesive composed of a mixture of water soluble alkylene oxide copolymers, which attaches the reinforcement material to the stapler reload and anvil.

3.3.2.2 Indications

ECHELON ENDOPATH Staple Line Reinforcement is indicated for use in surgical procedures in which soft tissue transection or resection with staple line reinforcement is needed. ECHELON ENDOPATH Staple Line Reinforcement can be used for reinforcement of staple lines during lung resection and bariatric surgical procedures. The device can also be used for reinforcement of staple lines during gastric, small bowel and colorectal procedures.

3.3.2.3 Labeling of Study Products

The ECHELON SLR has received 510(k) clearance in the United States from the Food and Drug Administration (FDA). The study device will use the cleared labeling. The Sponsor requires no additional labeling in this study.

3.3.2.4 Accountability of Study Products

The ECHELON SLR will be provided to the participating institutions. Devices will be tracked using shipping receipts and device accountability logs and all device returns will be managed by contacting EES. Devices provided for the study must be kept in a secure area and used only for treating subjects participating in the study, in accordance with the protocol. If applicable, the study device inventory must be available for periodic inspection/verification.

3.3.3 Prior and Concomitant Therapy

Subjects will be assessed for prior medication therapy history (30 days prior) during Visit 1 (Screening Visit).

Any medications administered during the study must be documented on the concomitant medication eCRF except for medications used by the site as standard of care for surgical procedures (i.e., standard perioperative medications, including anesthesia, etc.).

3.3.3.1 Restricted Therapy

Treatments restricted during the course of this study because of potential influence on study variables include:

- Concurrent treatment with medications that the investigator deems could have an influence on wound healing, unless deemed in the subject's best medical interest and then it would be allowed (rationale for use must also be collected).

3.4 STUDY VARIABLES

Specific variables assessed in the study are provided in the following sections. Refer to Section 3.5 Schedule of Events for the time when the study variables will be collected throughout the course of the study.

3.4.1 Demographic and Baseline Characteristics

The following will be collected preoperatively:

- Age (years);
- Gender;
- Race;
- Ethnicity;
- Body weight (kg or lbs; no shoes);
- Body height (cm or in; no shoes);
- American Society of Anesthesiologists (ASA) Physical Status Classification;
- Incidence and location of cancer and occurrence of pre-surgical radiation/chemotherapy within 90 days prior to surgery (when and how many doses), if applicable.
- Review and collection of medical history and surgical history including the following:
    - Surgical procedure to be conducted (and technique used), including primary indication for surgery;
    - Smoking history; and
    - Tumor details (including staging information), if applicable.

3.4.2 Surgical Variables

The following will be recorded preoperatively, intraoperatively, or postoperatively:

- Date/time of hospital admission;
- Endocutter and reload used (type, name, and color [for reload]) for each firing during the procedure along with which firings are associated with the study device;
- Total number of study devices used during the procedure;
- Number of study device(s) replaced during surgery due to slipping or bunching or not properly loaded onto stapler cartridge (these are product complaints and should be reported; refer to section 7.0);
- If any intervention used for intra-operative bleeding on the staple line, capture type and number of interventions used;
- Occurrence of blood transfusion (record the total required units of blood, rationale, and if related to staple line);
- If applicable, date(s) of chest tube placement and removal, daily volume and characteristics of chest tube drainage;
- Air leak duration in lung resection procedures;

- Procedure duration, defined as first skin incision to final skin closure;
- Volume of estimated intra-operative blood loss;
- Conversion to open, if it occurs (with rationale);
- For the gastric procedure group, if it occurs:
    - Bleeding (defined in section 2.1);
    - Leak (occurrence of intra-operative or post-operative gastrointestinal leak related to the staple line as documented intra-operatively, by clinical exam, or radiographically);
    - Stricture (occurrence of stricture documented radiographically or by endoscopy along the staple line);
- For the lung resection procedure group, if it occurs:
    - Prolonged air leak related to the staple line greater than postoperative day 7 (procedure=day 0); and
    - Empyema (purulent fluid collection in the pleural space documented radiographically, excluding chronic empyema.
- If available, video recordings (refer to Section 4.3). Video footage will not be considered source documentation for purposes of data collection for this study. Video may be used for the assessment of:
    - Number of study device(s) replaced during surgery due to slipping or bunching;
    - Endocutter and reload used (type, name, and color [for reload]) for each firing during the procedure along with which firings are associated with the study device;
    - If intervention used for intra-operative bleeding on the staple line, capture length of time, type and number of interventions used; and
    - Total video operative time and breakdown of time by major steps of the procedure;
- Concomitant procedures, if applicable (defined as any medical or surgical procedure beyond activities associated with primary study procedure);
- Concomitant medication usage, except for medications used by the site as standard of care for surgical procedures;
- Date/time of hospital discharge.

3.4.3 Device Questionnaire

Investigators will be asked to answer a non-validated device questionnaire related to his/her experience using the ECHELON SLR. The questionnaire will be completed by the Investigators as soon as possible after the investigator's 1st, 3rd, and 5th procedure, preferably on the same day. The questionnaire responses will then be transcribed onto eCRFs.

3.4.4 Safety Data Variables

All device-related and procedure-related AEs will be collected and captured as outlined in

Section 6.0.

3.5 SCHEDULE OF EVENTS

Table 1: Schedule of Events

Activity	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Unscheduled Visit, if applicable[a]
	Screening Visit (-56 to -1 Days)[a]	Procedure (Day 0) Through Discharge Visit	Post Procedure Follow Up Visit (28 ± 14 Days)[b]	Post Procedure Follow Up Visit (70 ± 14 Days)[b]	Post Procedure Follow Up Visit (135 ± 14 Days)[b]	
Informed consent	X					
Demographics (age, gender, race, and ethnicity)	X					
Height and weight (both with no shoes)	X					
Medical and surgical history (including diagnosis)	X	X				
Review of inclusion/exclusion criteria	X	X				
Surgical data collected for evaluation		X				
Collect device questionnaire[c]		X				
Concomitant procedures conducted in addition to study procedure		X	X	X	X	X
Concomitant medications (30 days prior)	X	X	X	X	X	X
Device-related and procedure-related AEs		X	X	X	X	X
Video Assessment[d]		X				
Unscheduled visits (if applicable)						X
Subject completion/discontinuation		X	X	X	X	X

[a] The screening activities will occur prior to the study procedure and may be completed on the day of the procedure;
[b] This can be either an office visit or telephone follow-up;
[c] The device questionnaire will be completed after an investigator's 1st, 3rd and 5th procedure;
[d] Video assessment for each participating subject, as applicable.

AE = adverse events

3.6 STUDY PROCEDURES

3.6.1 Visit 1 – Screening (may occur over visits within 8 weeks of Visit 2)

Prospective subjects will be provided with the study information including the ICD. The subject must be given ample time to review and sign the ICD. The screening activities noted in Section 3.5 will occur prior to the study procedure.

3.6.2 Visit 2 – Procedure Through Discharge Visit

Pre-procedure

The following must be performed prior to the surgical procedure:

- Updates to medical/surgical history;
- Confirm inclusion and exclusion criteria.

Intra-operative and Post-operative

Data collected during and after the procedure as defined in Section 3.4.

3.6.3 Visit 3 – Post-procedure Follow-up Visit

After the surgery, subjects will have a follow-up visit approximately 28 days later (+/- 14 days). This visit can be either an office visit or a telephone follow-up. Data to be collected is defined in Section 3.5.

3.6.4 Visit 4 – Post-procedure Follow-up Visit

After the surgery, subjects will have a follow-up visit approximately 70 days later (+/- 14 days). This visit can be either an office visit or a telephone follow-up. Data to be collected is defined in Section 3.5.

3.6.5 Visit 5 – Post-procedure Follow-up Visit

After the surgery, subjects will have a follow-up visit approximately 135 days later (+/- 14 days). This visit can be either an office visit or a telephone follow-up. Data to be collected is defined in Section 3.5.

3.6.6 Unscheduled Visit(s)

Any unscheduled visit between Visit 2 and Visit 5 will be documented including the reason for the visit. These visits can be either an office visit or a telephone follow-up.

4.0 DATA MANAGEMENT AND INTEGRITY

4.1 DATA COMPLETION AND RECORD KEEPING

4.1.1 Source Documents

Source documents are documents on which information regarding subjects is first recorded, including printed, optical, 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; radiographs; device accountability records; photographic negatives; and records kept at the investigation site, at the laboratories and at other departments involved in the clinical study. Source document worksheets may also be used to facilitate data collection and entry into eCRFs.

Source documents must be retained by the Investigator as part of the subject's study 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. Any deviations from the study protocol or procedures should be recorded in the source documents. The Investigator will retain originals of all source documents, subject consent forms, and study data per site policy.

4.1.2 Electronic Data Capture

An 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 [redacted] 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. [redacted]

4.1.3 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 and 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 PI is responsible for reviewing and approving each completed eCRF. Assurance of overall review and approval will be documented by the PI electronically signing each subject's electronic casebook.

4.1.4 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) was made to the eCRFs will be automatically captured in the audit trail within Medidata Rave.

4.1.5 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.

4.1.6 Record Retention, Inspection, and Custody

The PI must maintain all documentation related to the study until notified by the Sponsor. The PI will allow representatives of the Sponsor or other 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 study records will be maintained in a confidential manner. Study reports will not identify subjects by name. These reports may be submitted to 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 before the transfer occurs.

4.2 MEDICAL DICTIONARY CODING

Medical dictionary coding of medical history, verbatim AEs, and concomitant medication terms captured on eCRFs will be performed using a coding thesaurus algorithm. The Medical

Dictionary for Regulatory Activities (MedDRA) and World Health Organization Drug Dictionary will be used after data entry and query resolution, via auto-encoding and interactive coding processes.

4.3 VIDEO RECORDING AND ANALYSIS

Video will be used in an exploratory analysis to validate the utility of video analysis to assess several study variables. Video footage will not be considered source documentation for purposes of data collection for this study. C-SATS, part of the Johnson & Johnson Institute, is a performance management system for healthcare professionals that may be used to assess and improve performance continuously, accurately, and objectively. In this study, the C-SATS platform may be used for video upload and analysis.

Videos of the surgical procedure will be recorded at applicable investigational sites. Videos should be of the entire procedure, as per physician/hospital standard of care.

Upon completion of the surgical procedure, the video will be sent to the Sponsor via one of the following methodologies, based on local requirements:

- Upload videos to Sponsor from the hospital source video or hospital cloud storage; or
- Send video via encrypted hard drive to the Sponsor.

Specific instructions for each delivery method will be included in the Investigator Site File.

The following variables will be reviewed through videos obtained during the procedure (as mentioned in Section 3.4.2): 1) counts of number of study device(s) replaced during surgery due to slipping or bunching, 2) endocutter and reload used (type, name, and color [for reload]) for each firing during the procedure along with which firings are associated with the study device, 3) if intervention used for intra-operative bleeding on the staple line, capturing length of time, type and number of interventions used, and 4) total video operative time will be captured. Additional post-hoc data collection and analysis of other variables from the videos may be performed.

The video collected will be used for an exploratory comparison analysis to data entered into eCRFs (based on source document worksheets, subject files, and/or hospital records), in order to validate the use of video for possible endpoint assessment in future studies.

Any issues observed by independent reviewers that may constitute a device deficiency shall be reported following the sponsor's product complaints reporting process for medical devices. For any discrepancies noted as a result of the comparison analysis, only the site-reported data will be considered for purposes of study endpoint assessment, as the videos are not considered source documentation for purposes of study data collection.

In order to maintain independence of the video reviewers, access to the EDC database will not be granted to the video reviewers.

Participation with video recording of the surgical cases is not mandatory. Surgeons or subjects who decide to opt out will still be included in the study.

4.4 DATA QUALITY ASSURANCE

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate sites, 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 monitoring visits and periodic reviews; any discrepancies will be resolved with the Investigator or designees, as appropriate.

4.4.1 Site Personnel Training

Prior to completing any study-related assessments, the PI, Sub-Investigator(s), Study Coordinator, and other designated staff (as applicable) will be trained on study execution, data collection, and procedures specific to this clinical protocol.

4.4.2 Monitoring

This study will be monitored by the Sponsor or its representative to ensure:

- The rights and well-being of the subjects are protected;
- The 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 agreed to by the Sponsor and investigators. Monitors will comply with established written standard operating procedures as well as procedures specified by the Sponsor for monitoring this study as characterized in the monitoring plan for this study.

4.4.3 Quality Assurance

The extent and nature of quality assurance audits will be predetermined and based on considerations such as the regulatory classification, objective, and complexity of the study. Any audits performed will comply with established written standard operating procedures and the audit plan for this study.

4.5 PROTOCOL DEVIATIONS

A deviation (any activity conducted outside the parameters established by the protocol) can be identified from a number of sources. Potential sources for identification of deviations 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 in the source documentation as well as the eCRF. The PI will report protocol deviations to the IRB as required by the IRB procedures.

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

The Sponsor will be responsible for the analysis of data from this protocol. A detailed Statistical Analysis Plan (SAP) will be written and approved prior to final database lock. The SAP will describe all planned analyses based on the statistical design of this study and the subsequent data collected. A brief overview of key statistical analyses is provided below.

5.1 STUDY DESIGN

Study design is described in Section 3.1.

5.2 TREATMENT ASSIGNMENT

This is a single-arm study where all enrolled subjects will have the ECHELON SLR utilized during the surgical procedure.

5.3 INTERVAL WINDOWS

Interval windows for the purpose of analysis in this study will not be defined outside of those already specified in the protocol for visit scheduling. The final visit occurs approximately 19 weeks after surgery, thus no interval windows need to be defined given the absence of long-term follow-up in this study. The Schedule of Events specifies a window of 14 days around the scheduling of the follow-up visits, and any information entered in the eCRFs at this visit will correspond to the associated visit. There will be no assigning of observations to time points outside of the visit to which they are recorded in the eCRFs.

5.4 PRIMARY AND SECONDARY ENDPOINTS AND ASSOCIATED HYPOTHESES

All study endpoints are described in Section 2.1 through Section 2.3. The following hypotheses will be evaluated for the primary endpoint for gastric procedures:

$$H_0: p_G \geq 14.0\%$$

$$H_1: p_G < 14.0\%$$

Where p_G is the percentage of subjects experiencing at least one occurrence of bleeding, leak, or stricture through 70 days. A 95% confidence interval will be calculated for p_G based on the sample proportion of subjects experiencing the endpoint using the Normal approximation to the Binomial distribution and the upper limit of this confidence interval will be compared to 14.0% to evaluate the above hypotheses. A p-value will be determined based on the same Normal approximation methodology.

A similar methodology will be applied to the data observed in lung procedures to evaluate the following hypotheses:

$$H_0: p_L \geq 12.0\%$$

$$H_1: p_L < 12.0\%$$

Where p_L is the percentage of subjects experiencing at least one occurrence of prolonged air leak or empyema through 70 days.

5.5 LEVELS OF SIGNIFICANCE

Each of the sets hypotheses above will be evaluated using a one-sided significance level of 0.025 and the overall level of significance across the study will be controlled at a value that does not exceed 0.05. Estimation of all additional endpoints will be performed using 95% confidence intervals.

5.6 ANALYSIS SETS

The summary of all performance and safety endpoints will be performed on the set of subjects in whom the ECHELON SLR is utilized during the surgical procedure. The summary of all primary and secondary endpoints will be performed by procedure group and in total.

5.7 SAMPLE SIZE JUSTIFICATION

For the gastric procedure group, a sample size of at least 99 subjects is required to have a minimum of 80% power for rejecting the null hypothesis when the expected rate of the primary endpoint is 7% based on current available literature[1,2]. Similarly, for the lung resection group, a sample size of at least 116 subjects is required to have a minimum of 80% power for rejecting the null hypothesis when the expected rate of the primary endpoint is 6% based on current available literature[3]. Each calculation is determined using the Normal approximation with a one-sided significance level of 0.025 and makes the assumption of a 20% reduction in the expected rate of the primary endpoint with the ECHELON SLR. The

performance goal-based hypotheses specified in Section 5.4 are based on establishing acceptable initial performance of the ECHELON SLR by ruling out a doubling of the expected risk that has been reported in the literature for these procedures.

Accounting for an anticipated dropout rate as high as 12.5% in each procedure group leads to an initial planned sample size of 112 subjects in the gastric group and 131 subjects in the lung resection group.

Given the lack of available clinical data on the performance of the ECHELON SLR, an adaptive approach to sample size re-estimation will occur after approximately 50% of the originally planned sample size has been enrolled into each procedure group. The purpose of this interim analysis will be to estimate the rate of the primary endpoint in each group or concurrently to estimate the size of the relative reduction of this endpoint relative to the values reported in current literature. The current sample size calculation assumes an expected background rate of 7% in the gastric group, 6% in the lung resection group, and that a 20% relative reduction will be observed with the ECHELON SLR. Based on the values observed at the interim analysis time points for each group, the within-group sample sizes will be re-estimated. A sample size of 200 subjects has been set as the maximum sample size that will be pursued following the interim analysis and sample size re-estimation process in the gastric group and a maximum of 231 subjects has been set in the lung resection group.

The sample size re-estimation for each group will apply the methodology described in Lan and Trost[4] and Wang, Keller, and Lan[5]. Following that methodology, the prespecified conditional power lower limit for futility is set at 10%, and the upper limit for maintaining the original sample size is set at 80%. Specifically, if the conditional power evaluated at the time of the interim analysis is ≤ 0.10, the trial within that procedure group will be stopped for futility and the null hypothesis will be accepted. If the conditional power is ≥ 0.80, then the study will continue to its originally planned completion with no sample size adjustment. If the conditional power is between 0.10 and 0.80, the sample size will be increased so as to maintain the conditional power at a target of 0.80 under the current trend of the data, up to the maximum values specified above.

As discussed in Lan and Trost, given that the lower limit of conditional power for futility is at least 0.10, the Type I error rate is controlled at the nominal level, and no adjustment to the planned significance level of 0.025 is required under this approach.

5.8 DATA MONITORING COMMITTEE

There are no plans to utilize a data monitoring committee during this study.

5.9 ANALYSES TO BE CONDUCTED

5.9.1 General Conventions

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. Confidence intervals will also be provided for procedure-related variables.

5.9.2 Disposition of Study Subjects

Subject disposition will be summarized in total and by procedure group using counts and percentages. The number and percentage of subjects completed and discontinued will be tabulated along with the specific reasons for discontinuation.

5.9.3 Demographic, Baseline, and Surgical Characteristics

Summary statistics of subject demographics (age, gender, race and ethnicity) will be presented in total and by procedure group. Similar summaries will also be provided for baseline and surgical characteristics including body mass index, surgical procedure, smoking history, ASA physical status classification, procedure duration, and additional surgical data outlined in earlier sections.

5.9.4 Primary and Secondary Endpoint Analyses

Within each procedure group, the number and percentage of subjects experiencing an occurrence of the primary endpoint will be summarized and a 95% confidence interval for each rate will be estimated. The performance goal hypotheses will be tested based on methodology as described above in Section 5.4.

The number and percentage of subjects experiencing each component of the composite endpoint will be summarized in each procedure group.

All device-related and procedure-related AEs reported during the study will be coded to MedDRA. All AEs will be summarized by MedDRA system organ class and preferred term by procedure group and in total. Separate summaries will be provided for device-related and procedure-related AEs. Serious AEs will be summarized in a similar manner.

Counts and percentages will be provided for usability data collected via surgeon questionnaire and summary statistics will be provided for the number of study devices attempted and used during the surgical procedure.

5.9.5 Plans for Interim Analyses

One interim analysis in each procedure group is planned for sample size re-estimation. Details are provided in Section 5.7 above. Study enrollment may continue while the interim analysis is ongoing.

5.9.6 Handling of Missing Data

All summaries will be performed only on subjects undergoing the scheduled 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 for the primary evaluation of the hypotheses specified above. Sensitivity analyses will be detailed in the SAP that will be designed to assess the robustness of the primary study conclusions to missing data or incomplete data on early terminated subjects.

5.9.7 Subgroup Analyses

Descriptive summaries are planned to be provided for each procedure within the lung resection group (lobectomy, segmentectomy, etc.). Subgroup analyses may be performed for additional groups pending the distributions of baseline demographic or clinical characteristics. These analyses will be exploratory, and summary statistics for the procedure-related parameters will be provided for each subgroup.

6.0 ADVERSE EVENTS

All adverse events considered unlikely, possibly, probably, or causally related to the device or the procedure will be collected during this study.

6.1 DEFINITIONS

6.1.1 Adverse Event

An AE is defined as any untoward medical occurrence, regardless of its relationship to the study device or the study procedure. An untoward medical occurrence includes any new, undesirable medical experience or worsening of a pre-existing condition, which occurs throughout the duration of the clinical study.

6.1.2 Adverse Device Effect

An adverse device effect (ADE) is an AE related to the use of a study device. This includes any AE resulting from insufficient or inadequate IFU, deployment, implantation, installation, operation, or any malfunction of the study device. An ADE may also include any event resulting from user error or from intentional misuse of the study device.

6.1.3 Serious Adverse Event

It is the Investigator's responsibility to determine the "seriousness" of a reportable AE.

A SAE is defined as an AE (as defined in Section 6.1.1) that results in any of the following:

- Death;
- A life-threatening illness or injury;
- A permanent impairment of a body structure or a body function;
- Required in-patient hospitalization or prolongation of existing hospitalization;
- Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; or
- Led to a fetal distress, fetal death, or a congenital abnormality or birth defect.

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

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a SAE.

6.1.4 Serious Adverse Device Effect (SADE)

A serious ADE (SADE) is an ADE that has resulted in any of the consequences characteristic of a SAE or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstance had been less opportune.

6.1.5 Unanticipated Serious Adverse Device Effect (USADE)

An unanticipated serious adverse device effect (USADE) is an effect which, by its nature, incidence, severity or outcome, has not been identified. An anticipated SADE is an effect which by its nature, incidence, severity, or outcome, has been identified in the IFU.

6.1.6 Pre-existing Condition

A pre-existing condition is defined as a medical condition that is present at the initiation of the study and is to be reported as part of the subject's medical history with a listed start date. Any pre-existing condition that has worsened in intensity, frequency, or the character of the condition should be recorded as a new AE on the AE eCRF, as an exacerbation of the pre-existing condition and the start date will be recorded as the time when the exacerbation occurred.

6.2 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 AE:

- **MILD:** Awareness of signs or symptoms, but does not interfere with the patient's usual activity, or is a transient event that resolves without treatment and with no sequelae.
- **MODERATE:** A sign or symptom, which interferes with the patient's usual activity.
- **SEVERE**: Incapacity with inability to do work or usual activities.

6.3 RELATIONSHIP OF ADVERSE EVENTS

It is the Investigator's responsibility to assess the relationship of a reportable AE (as defined in Section 6.1.1). Only AEs considered unlikely, possibly, probably, or causally related to the study procedures or the ECHELON SLR device are to be recorded in the eCRF and reported to the Sponsor.

The following guidelines should be used in determining the relationship of an AE in the study:

- **Not related** – Relationship to the procedures or device can be excluded when:
    - The event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
    - The event has no temporal relationship with the use of the device or the procedures;
    - The event does not follow a known response pattern to the device (if the response pattern is previously known) and is biologically implausible;
    - The discontinuation of the device application or the reduction of the level activation/exposure (when clinically feasible) and reintroduction of its use (or increase of the level of activation/exposure), does not impact on the event;
    - The event involves a body site or an organ not expected to be affected by the device or the procedure;
    - The event can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors);
    - Harms to the subject are not clearly due to use error; or
    - To establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedure and the event.
- **Unlikely** – The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- **Possible** – The relationship with the use of the device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/condition and/or an effect of another device, drug, or treatment). Cases where relatedness cannot be assessed, or no information has been obtained

should also be classified as possible.

- **Probable** – The relationship with the use of the device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
- **Causal relationship** – The event is associated with the device or with procedures beyond reasonable doubt when:
    - The event is a known side effect of the product category the device belongs to or of similar devices and procedures;
    - The event has a temporal relationship with the device uses/application or procedures;
    - The event involves a body-site or organ that:
        - The device or procedures are applied to or is adjacent to;
        - The device or procedures have an effect on;
    - The event follows a known response pattern to the medical device (if the response pattern is previously known);
    - The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible);
    - Other possible causes (e.g. an underlying or concurrent illness/clinical condition and/or an effect of another device, drug, or treatment) have been adequately ruled out;
    - Harm to the subject is due to error in use; or
    - To establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedure and the event.

6.4 REPORTING PROCEDURES FOR ADVERSE EVENTS

6.4.1 Recording Adverse Events

The Investigator will record all AEs (both AEs and SAEs) considered attributable (relationship of possible, probable, causal relationship) to the study procedure or the ECHELON SLR in the source documents and eCRF.

Standard medical terminology should be used when recording AEs. In addition, the following information should be recorded:

- Onset date;
- Resolution date or date of death;
- Severity of the event;
- Indication of whether the event is serious;
- Relationship of AE to the device used in the study;
- Relationship of AE to the study procedure;
- Action taken;
- Event status; and
- Was AE anticipated or not (only for SAEs).

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

exhausted. All AEs that are unresolved at study completion (or at the last visit completed for early withdrawal subjects) will be recorded as ongoing at study end.

6.4.2 Reporting Adverse Events

The Investigator is required to report AEs to the Sponsor within two weeks from when the study site becomes aware of the event. All AEs must be reported on the AE eCRF and be documented in a timely manner throughout the study duration.

6.4.3 Reporting Serious Adverse Events

Any AE that the Investigator determines to be a SAE must be reported by the study site within 72 hours of becoming aware of the event to the Sponsor by completing the AE eCRF. A notification containing the pertinent data will be automatically generated by the EDC system and forwarded to the Sponsor. If applicable, supporting SAE documentation should be de-identified and provided to the Clinical Trial Leader. 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 per their IRB procedures.

7.0 PRODUCT COMPLAINTS

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, labeling, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. A product complaint may or may not be associated with an AE/SAE.

7.1 REPORTING PRODUCT COMPLAINTS FOR MARKETED DEVICES

7.1.1 Reporting of Approved EES Marketed Devices

All product complaints related to devices in the procedure shall be documented throughout the clinical study. Product complaints related to an EES-manufactured ECHELON SLR must be reported to the Sponsor in a timely manner and no later than 24 hours after becoming aware of the event. When a sponsor representative becomes aware of a product complaint, the Product Complaint Team must be notified within 24 hours after becoming aware of the event. [redacted]

The sites will report Product Complaints by completing the Product Complaint Form. If a product complaint is related to a safety event, the site must complete an AE eCRF as well. One copy of the processed form should be kept on-site and the device should be retained. Sponsor representatives will organize collection of the device for evaluation as needed.

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