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A Prospective, Single-Arm Multi-Center Study of the ENSEAL® X1 Curved Jaw Tissue Sealer and Generator G11 in Upper Gastrointestinal, Lower Gastrointestinal, and Gynecological Procedures

Trial Number: ENG_2019_01

Document	Effective Date
Original	01 APR 2020
Amendment 1	15 MAY 2020
Amendment 2	10 SEP 2020
Amendment 3	01 MAR 2021
Amendment 4	16 JUL 2021
Amendment 5	11 NOV 2022

Sponsor:	Ethicon Endo-Surgery, Inc. 4545 Creek Road Cincinnati, Ohio 45242
Regulatory Classifications:	Class II in the United States and Class IIb in European Union and United Kingdom for both devices
Name of Finished Product(s):	ENSEAL® X1 Curved Jaw Tissue Sealer Generator G11
Sponsor's Medical Monitor:	Giovanni A. Tommaselli, M.D. Medical Director LCM Compliance 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.

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PROTOCOL SIGNATURE PAGE

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Approvals:

KATHRINE LORENZ

Digitally signed by KATHRINE LORENZ
DN: c=US, o=JNJ, ou=Subscribers, 0.9.2342.19200300.100.1.1=7354, cn=KATHRINE LORENZ
Reason: I am approving this document.
Date: 2022.11.14 11:11:19 -05'00'
Adobe Acrobat version: 2020.013.20064

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.

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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) / 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.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

_____

Site Identification Number

CLINICAL STUDY PROTOCOL SYNOPSIS

Regulatory Classification:	Class II in the United States and Class IIb in European Union and United Kingdom for both devices
Indication:	**ENSEAL® X1 Tissue Sealers (ENSEAL X1)** The ENSEAL X1 devices are bipolar electrosurgical instruments for use with an electrosurgical generator. They are intended for use during open or laparoscopic surgical procedures to cut and seal vessels, and to cut, grasp and dissect tissue during surgery. Indications for use include open and laparoscopic general, gynecological, urologic, thoracic, and ENT surgical procedures or any procedure where vessel ligation (cutting and sealing), tissue grasping, dissection, and division of vessels, lymphatics, and tissue bundles is performed (e.g. bowel resections, hysterectomies, gall bladder procedures, Nissen Fundoplication, adhesiolysis, and oophorectomies). The devices can be used on vessels up to and including 7 mm and bundles as large as will fit in the jaws of the instruments. The ENSEAL X1 Tissue Sealers have not been shown to be effective for tubal sterilization or tubal coagulation for sterilization procedures. **Generator G11 (GEN11)** The GEN11 provides radiofrequency power to drive ENSEAL electrosurgical instruments that are used during open or laparoscopic general and gynecological surgery to cut and seal vessels and to cut, grasp, and dissect tissues. In addition, the generator provides power to drive HARMONIC ultrasonic surgical instruments that are indicated for soft tissue incisions when bleeding control and minimal thermal injury are desired. ENSEAL and HARMONIC instruments, when used with the GEN11, have not been shown to be effective for sterilization procedures or tubal coagulation.
Objective(s):	The primary objective of this study is to demonstrate the acceptable performance and safety of the ENSEAL X1 and GEN11 devices when used per the instructions for use (IFU).
Overview of Study Design:	This prospective, single-arm, multi-center study will collect clinical data in a post-market setting by procedure group (upper gastrointestinal [GI], lower GI, and gynecological). Investigators will perform each procedure using the device in compliance with their standard surgical approach and the ENSEAL X1 and GEN11 IFUs. Subjects will be consented and screened anytime during a period of 8 weeks prior to the date of surgery. Subjects will be considered enrolled when the ENSEAL X1 device has been attempted to be used for a vessel transection during upper GI, lower GI, or gynecological procedures. All enrolled subjects will be followed post-operatively through discharge and again at 28 days (± 14 days) post-surgery; therefore, from the surgery date to study exit, the duration will be approximately 6 weeks.

Number of Subjects:	In order to achieve a total of 230 vessel transections for analysis with a minimum of 27 vessel transections in each group (including 4 subgroups in upper GI procedure), a minimum of 133 subjects (maximum of 149 subjects) will be included in the study from up to 16 surgery centers in the United States and/or European Union and/or United Kingdom. The minimum number of subjects is determined based on the number of subjects enrolled at the time of amendment 5 and projection of subjects needed to achieve a minimum of 27 vessels per group, deemed to be adequate to ensure optimum representation of each of the procedure groups in the whole study sample. The enrollment is planned with the following procedure targets:
	• A minimum of 77 subjects enrolled to a maximum of 89 subjects enrolled for upper GI procedures to achieve 27 vessel transections in each of the four subgroups. Subjects will be enrolled to the following subgroups with corresponding enrollment restrictions:
	  ○ A minimum of 14 subjects enrolled to a maximum of 17 subjects enrolled for fundoplication (Nissen, anterior or posterior [Toupet]) or hiatal hernia procedures);
	  ○ A minimum of 27 subjects enrolled to a maximum of 30 subjects enrolled for gall bladder procedures;
	  ○ A minimum of 10 subjects enrolled to a maximum of 13 subjects enrolled for sleeve gastrectomy procedures;
	  ○ A minimum of 26 subjects enrolled to a maximum of 29 subjects enrolled for small intestine resection procedures (also includes Roux-en-Y gastric bypass [RYGB] and biliopancreatic diversion with duodenal switch [BPD/DS]);
	• A minimum of 28 subjects enrolled to a maximum of 30 subjects enrolled for lower GI procedures (e.g., large intestine resections); and
	• A minimum of 28 subjects enrolled to a maximum of 30 subjects enrolled for gynecological procedures (hysterectomies associated with oophorectomies).

Criteria for Inclusion:	Subjects satisfying the following criteria will be considered eligible for enrollment in this study: 1. Primary laparoscopic or open procedure (upper GI, lower GI, or gynecological) where at least one vessel is planned to be transected by the ENSEAL X1 device per the IFU; 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: 1. Physical or psychological condition which would impair study participation; or

	2. Enrollment in a concurrent interventional clinical study that could impact the study endpoints.
Test Product:	ENSEAL® X1 Curved Jaw Tissue Sealer (Product Codes: NSLX125C, NSLX137C, or NSLX145C) and Generator G11 (GEN11).
Reference Therapy/ Product:	No comparator product is being used in this study.
Duration of Treatment:	Subjects will be exposed to the ENSEAL X1 device during the procedure and while the device is used as indicated in the IFU. The device nor any device components remain in the patient after use.

Criteria for Evaluation:	The primary performance endpoint will be:
	• Achievement of Grade 3 or lower hemostasis for each vessel transection (per the grading scale below):
	  ○ Grade 1: no bleeding at transection site;
	  ○ Grade 2: minor bleeding at transection site, no intervention needed;
	  ○ Grade 3: minor bleeding at transection site, mild intervention needed, use of compression, basic energy devices (monopolar and/or bipolar) and/or touch-ups with ENSEAL X1; or
	  ○ Grade 4: significant bleeding (e.g., pulsatile blood flow, venous pooling) requiring intervention such as extensive coagulation or ligation with use of additional hemostatic measures (e.g., hemoclips, staples, sutures, fibrin sealants, other advanced energy products);
	The secondary performance endpoints will be:
	• Distribution of 5-point scale scores for various tasks completed by the ENSEAL X1 device (adhesiolysis, lymphatics or tissue bundles divided, tissue grasping, tissue cutting, or tissue dissection);
	• Distribution of hemostasis grading scale for each vessel transected; and
	• Type, name, and number of additional hemostasis products required to achieved hemostasis for Grade 4 vessel transections.
	The safety endpoint will be:
	• Occurrence of device-related adverse events (AEs).

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 ENSEAL X1 device is utilized during the surgical procedure. The summary of all performance and safety endpoints will be performed by procedure group, procedure subgroup, and on the entire pooled set of subjects.

Sample Size Determination

A sample size of at least 230 vessel transections is required to have a minimum of 90% power for rejecting the null hypothesis that the rate of Grade 3 or lower hemostatic transections is less than 87.5% when the expected rate of Grade 3 hemostatic transections is at least 94.0% based on exact binomial test and a one-sided significance level of 0.025. The hemostatic transection grades for vessels are assumed to be independent within a subject and a procedure.

In order to achieve a total of 230 vessel transections for analysis with a minimum of 27 vessel transections in each group (including 4 subgroups in upper GI procedure), a minimum of 133 subjects (a maximum of 149 subjects) will be enrolled in the study.

The original sample size of the study was based on the assumption of one vessel transection per subject. At the time of amendment 5 the number of transections per subject was estimated to be 1.9 on average. The primary endpoint and the study hypothesis are based on hemostasis of vessel transection; therefore, the number of subjects to be enrolled was updated to ensure 230 vessel transections.

Performance Analyses

The number and percentage of vessels where hemostasis is achieved (≤ Grade 3) will be summarized and an exact 95% confidence interval will be estimated for each procedure group (upper GI, lower GI, and gynecological), the six individual procedure subgroups, and in total. The performance goal hypothesis will be evaluated using the lower bound of the exact 95% confidence interval and a p-value will be calculated using exact binomial test. The 95% confidence interval will be estimated based on the Clopper-Pearson method. Counts and percentages will be provided for type, size, and number of vessels transected, grading scale distribution for all vessels transected, number of times ENSEAL X1 touch-ups were required, and incidence of requirement for additional measures to obtain hemostasis on vessels (other advanced energy devices or hemostatic measures).

Safety Analyses

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

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PROTOCOL-SPECIFIC ACRONYMS AND ABBREVIATIONS

Acronyms/Abbreviations	Terms
AE	Adverse event
ASA	American Society of Anesthesiologists Physical Status Classification System
EC	Ethics committee
eCRF	Electronic case report form
EDC	Electronic Data Capture
EES	Ethicon Endo-Surgery, Inc.
ENSEAL G2	ENSEAL® G2 Tissue Sealer
ENSEAL X1	ENSEAL® X1 Curved Jaw Tissue Sealer
GEN11	Ethicon Endo-Surgery Generator G11
FDA	Food and Drug Administration
GCP	Good clinical practice
GI	Gastrointestinal
ICD	Informed consent document
IFU	Instructions for use
IRB	Institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
OR	Operating room
PCF	Product complaint form
PHI	Protected health information
PMCF	Post-market clinical follow-up
RYGB	Roux-en-Y gastric bypass
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	Standard of care

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 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 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 up to sixteen surgery centers in the United States and/or European Union and/or United Kingdom 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 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).

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 monitor(s), change of telephone number(s)). The Investigator reports the protocol amendments to the IRB/EC as per their local requirements.

1.0 INTRODUCTION

The ENSEAL X1 device is a sterile, single-patient-use advanced bipolar surgical instrument intended for use during open or laparoscopic surgical procedures to seal and transect vessels up to and including 7mm in diameter and lymphatics, and to cut, grasp and dissect tissue during surgery.

ENSEAL X1 differs primarily in three ways from the earlier version of the device, the ENSEAL® G2 Tissue Sealer (ENSEAL G2).

1. The ENSEAL G2 relied on I-BLADE® Technology to provide compression along the device tip, whereas the ENSEAL X1 has a redesigned jaw that provides uniform compression without the need for an I-BLADE.
2. The ENSEAL G2 used a positive temperature coefficient technology to modulate energy flow and control temperature at the blade, whereas ENSEAL X1 uses electrical impedance feedback to intelligently monitor tissue conditions and modulate energy delivery to ensure effective sealing while minimizing tissue damage.
3. The ENSEAL G2 had an integrated seal-and-cut steps for use, whereas ENSEAL X1 has separated these into intuitive, simplified functions, so that surgeons may now seal without cutting, cut without sealing, or both seal and cut.

The ENSEAL X1 devices have undergone extensive preclinical testing to ensure that they are capable of producing strong and durable seals for vessels up to 7mm in diameter. Beginning in 2018, the open-surgery version, ENSEAL X1 Large Jaw, was successfully launched. Now, a laparoscopic version, ENSEAL X1 Curved Jaw (Figure 1) is being introduced to the market. With a shaft diameter of 5 mm, the device will be available in lengths of 25, 37, and 45 cm. The curved tapered tip of the device is designed for fine dissection, while being able to capture more tissue per bite with stronger grasping than the predicate device. The shaft can be rotated a full 360° for easier access to targeted tissue.

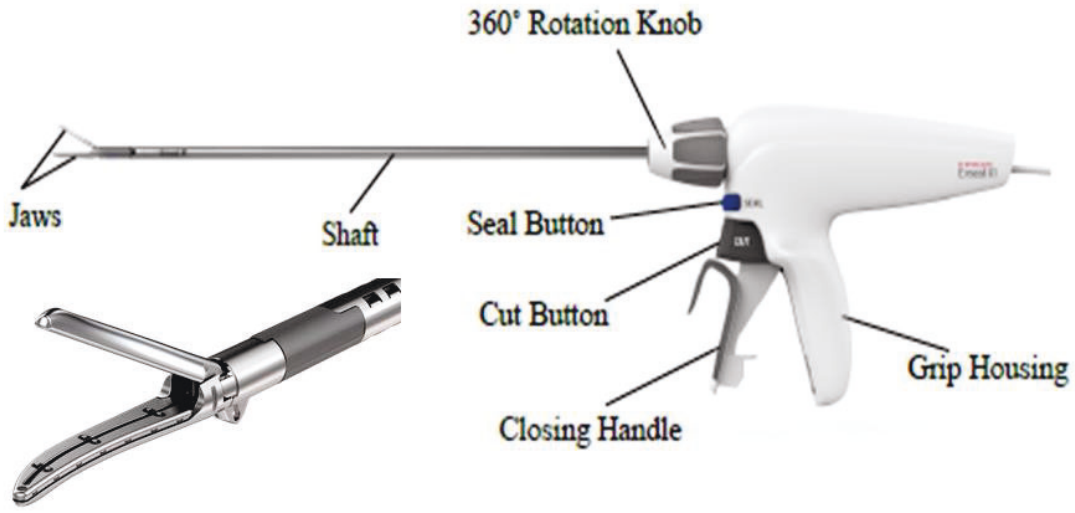

Figure 1: Image of the ENSEAL X1.

The GEN11 supplies energy to the HARMONIC and ENSEAL surgical instruments. It also has a touchscreen for easy setup and operation, and a high-resolution display with wider viewing angles. Software updates to ensure that the system is operating optimally are available via USB memory stick. The generator uses a touchscreen display interface and has a unique receptable

port that accepts either a HARMONIC or an ENSEAL instrument. Connectors (HGA11 for HARMONIC and EGA11 for ENSEAL) are used to enable the generator to power legacy instruments.

The ENSEAL X1 device includes several incremental enhancements of the same basic technology used with predicate devices. This study is being initiated to evaluate the subject devices when used per their instructions for use (IFU) in the following types of procedures: upper GI, lower GI, and gynecological.

2.0 STUDY OBJECTIVES

The primary objective of this study is to demonstrate the acceptable performance and safety of the ENSEAL X1 and GEN11 devices when used per the instructions for use (IFU).

2.1 PRIMARY PERFORMANCE ENDPOINT

A hemostasis grading scale was adopted from Siegel et al.[1] The primary performance endpoint will be:

- Achievement of Grade 3 or lower hemostasis for each vessel transection (per the grading scale below):
  - Grade 1: no bleeding at transection site;
  - Grade 2: minor bleeding at transection site, no intervention needed;
  - Grade 3: minor bleeding at transection site, mild intervention needed, use of compression, basic energy devices (monopolar and/or bipolar) and/or touch-ups with ENSEAL X1; or
  - Grade 4: significant bleeding (e.g., pulsatile blood flow, venous pooling) requiring intervention such as extensive coagulation or ligation with use of additional hemostatic measures (e.g., hemoclips, staples, sutures, fibrin sealants, other advanced energy products).

2.2 SECONDARY PERFORMANCE ENDPOINTS

The secondary performance endpoints will be:

- Distribution of 5-point scale scores for various tasks completed by the ENSEAL X1 device (adhesiolysis, lymphatics or tissue bundles divided, tissue grasping, tissue cutting, or tissue dissection). The scale will be a 5-point scale (very dissatisfied, dissatisfied, neither satisfied or dissatisfied, satisfied, or very satisfied) asking how satisfied the surgeon was with the use of the device for each of the tasks;
- Distribution of hemostasis grading scale for each vessel transected; and
- Type, name, and number of additional hemostasis products required to achieve hemostasis for Grade 4 vessel transections.

2.3 SAFETY ENDPOINT

The safety endpoint will be occurrence of device-related adverse events (AEs).

2.4 ADDITIONAL KEY DATA COLLECTED

Additional key data collected for evaluation in this study are:

- Procedure duration;

- Use of any other energy device (basic [monopolar and traditional bipolar], advanced bipolar, ultrasonic) in primary procedure (type, name, and number of device and reason for use), if applicable;
- Overall assessment questionnaire of how device performed in various tasks for lower GI/large intestine resection and gynecological procedures;
- Surgeon questionnaire administered once per investigator;
- Task questionnaire after each lower GI/large intestine resection and gynecological procedure;
- Generator questionnaire after each procedure for each GEN11 used;
- Surgical procedure conducted;
- Hospital stay duration;
- Name and number of vessels that were transected, surgeon determination of diameter size range (< 3 mm, 3 to 5 mm, and > 5 to 7 mm);
- Occurrence and location of cancer and occurrence of pre-surgical radiation/chemotherapy within 90 days prior to surgery, if applicable;
- Occurrence of vessel skeletonization;
- Presence of inflamed tissue, calcified tissues/vessels, atherosclerotic tissue, fibrotic tissue, or presence of adhesions, if applicable;
- Volume of estimated intra-operative blood loss;
- Occurrence of blood transfusion, if applicable (record the total required units of blood and rationale);
- Type of additional mild interventions (use of compression, basic energy devices [monopolar and/or bipolar] and/or touch-ups with ENSEAL X1) required to achieve hemostasis for Grade 3 vessel transections including number of times when ENSEAL X1 touch-ups were used; and
- Procedure-related AEs.

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 (upper GI, lower GI, and gynecological). Investigators will perform each procedure using the device in compliance with their standard surgical approach and the ENSEAL X1 and GEN11 IFUs.

Subjects will be consented and screened anytime during a period of 8 weeks prior to the date of surgery. Subjects will be considered enrolled when the ENSEAL X1 device has been attempted to be used for a vessel transection during upper GI, lower GI, and gynecological procedures. All subjects enrolled will be followed post-operatively through discharge and again at 28 days (± 14 days) post-surgery; therefore, from the surgery date to study exit, the duration will be approximately 6 weeks.

3.2 STUDY POPULATION

3.2.1 Enrollment

Subjects will be recruited from the existing patient population who plan to have a procedure from the proposed procedure groups (upper GI, lower GI, and gynecological)

utilizing consecutive screening and enrollment in an effort to generate a random and representative patient population sample. All eligible subjects (Sections 3.2.3 and 3.2.4) will be considered enrolled at the time when the ENSEAL X1 device has been attempted to be used for a vessel transection during one of the proposed procedure groups. Up to 16 surgery centers (United States and/or European Union and/or United Kingdom) will be selected as study sites. Each participating investigator is expected to perform a minimum of two procedures using the ENSEAL X1 device. A minimum of 133 subjects (maximum of 149 subjects) will be included in the study to achieve a total of 230 vessel transections. The enrollment is planned with the following procedure targets:

- A minimum of 77 subjects enrolled to a maximum of 89 subjects enrolled for upper GI procedures which will contain the following subgroups with corresponding enrollment restrictions:
    - A minimum of 14 subjects enrolled to a maximum of 17 subjects enrolled for fundoplication (Nissen, anterior or posterior [Toupet]) or hiatal hernia procedures);
    - A minimum of 27 subjects enrolled to a maximum of 30 subjects enrolled for gall bladder procedures;
    - A minimum of 10 subjects enrolled to a maximum of 13 subjects enrolled for sleeve gastrectomy procedures;
    - A minimum of 26 subjects enrolled to a maximum of 29 subjects enrolled for small intestine resection procedures (also includes RYGB and BPD/DS),
- A minimum of 28 subjects enrolled to a maximum of 30 subjects enrolled for lower GI procedures (e.g., large intestine resections); and
- A minimum of 28 subjects enrolled to a maximum of 30 subjects enrolled for gynecological procedures (hysterectomies associated with oophorectomies). The planned use of the ENSEAL X1 device should be for both the hysterectomy and oophorectomy steps of the procedures.

3.2.2 Screening Failures

All subjects signing consent who do not have at least one vessel transection attempted by ENSEAL X1 during their procedures will be recorded as screen failures. For subjects who are determined to be screen failures, only the relevant electronic eCRF pages (inclusion/exclusion criteria, demographics, AEs, subject completion/discontinuation) will be completed.

3.2.3 Inclusion Criteria

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

1. Primary laparoscopic or open procedure (upper GI, lower GI, and gynecological) where at least one vessel is planned to be transected by the ENSEAL X1 device per the IFU;
2. Willingness to give consent and comply with all study-related evaluations and treatment schedule; and

3. At least 18 years of age.

3.2.4 Exclusion Criteria

Subjects meeting the following criteria will be considered ineligible for enrollment in this study:

1. Physical or psychological condition which would impair study participation; or
2. Enrollment in a concurrent interventional clinical study that could impact the study endpoints.

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 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, which 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

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

3.3 STUDY PROCEDURES

3.3.1 Procedure Description

Elective upper GI, lower GI, and gynecological procedures where ENSEAL X1 is indicated for use will be performed per the institution's SOC. Only the principal investigator or sub-Investigator can use the device during the vessel transections. For the gynecological procedures, the planned use of the ENSEAL X1 device should be for both the hysterectomy and oophorectomy steps of the procedures.

3.3.2 Identity of Study Products

The ENSEAL X1 and the GEN11 are the study products for this study.

3.3.2.1 Device Description

ENSEAL X1

The ENSEAL X1 instrument is a sterile, single-patient-use surgical instrument to coagulate and transect vessels up to and including 7 mm in diameter, tissue and/or vascular bundles. This device is to be used for soft tissue only. The instrument consists of a grip housing assembly, a rotating shaft, a moveable jaw, and a knife. The instrument shaft can be rotated 360° to facilitate visualization and enable easy access to targeted tissue. The jaws are in a normally-opened position and can be partially or fully closed by squeezing the closing handle. The jaws are designed for grasping and holding targeted tissue when clamped. The ENSEAL X1 has separate seal and cut capabilities. The lower jaw of the ENSEAL X1 can be used in the open or closed position to deliver energy based on the electrode configuration and jaw design. Bipolar energy is delivered when the SEAL button on the device or the MIN foot pedal is pressed. Pressing the CUT button advances the knife the length of the jaws to cut the targeted tissue. The power cord is permanently attached to the device and connects the instrument to the generator. The ENSEAL X1 instrument is designed for use exclusively with the GEN11 software version 2016-1 or later, packaged separately.

GEN11

The GEN11 device supplies energy to the HARMONIC and ENSEAL surgical instruments. The generator uses a touchscreen display interface and has a unique receptacle port that accepts either a HARMONIC or an ENSEAL instrument. Connectors (HGA11 for HARMONIC and EGA11 for ENSEAL) are used to enable the generator to power legacy instruments.

3.3.2.2 Indications

ENSEAL X1

The ENSEAL X1 are bipolar electrosurgical instruments for use with an electrosurgical generator. They are intended for use during open or laparoscopic surgical procedures to cut and seal vessels, and to cut, grasp and dissect tissue during surgery.

Indications for use include open and laparoscopic general, gynecological, urologic, thoracic, and ENT surgical procedures or any procedure where vessel ligation (cutting and sealing), tissue grasping, dissection, and division of vessels, lymphatics, and tissue bundles is performed (e.g. bowel resections, hysterectomies, gall bladder procedures, Nissen Fundoplication, adhesiolysis, and oophorectomies). The devices can be used on vessels up to and including 7 mm and bundles as large as will fit in the jaws of the instruments.

The ENSEAL X1 have not been shown to be effective for tubal sterilization or tubal coagulation for sterilization procedures.

GEN11

The GEN11 provides radiofrequency power to drive ENSEAL electrosurgical instruments that are used during open or laparoscopic general and gynecological surgery to cut and seal vessels and to cut, grasp, and dissect tissues. In addition, the generator provides power to drive HARMONIC ultrasonic surgical instruments that are indicated for soft tissue incisions when bleeding control and minimal thermal injury are desired.

ENSEAL and HARMONIC instruments, when used with the GEN11, have not been shown to be effective for sterilization procedures or tubal coagulation.

3.3.2.3 Contraindications

ENSEAL X1

The efficacy of the ENSEAL X1 for the indication of contraceptive tubal coagulation (permanent female sterilization) has not been evaluated and is unknown. The design of the ENSEAL tissue sealing device is significantly different from bipolar designs that are marketed for the indication of contraceptive tubal coagulation. The design differences may affect the efficacy of the procedure and failure rates may not be comparable.

GEN11

The use of the GEN11 and the attached instruments are contraindicated when, in the judgement of the physician, radiofrequency or ultrasonic surgery would be contrary to the best interest of the patient. The instruments are not indicated for incising bone.

3.3.2.4 Labeling of Study Products

The ENSEAL X1 has received 510(k) clearance in the United States by the Food and Drug Administration (FDA) and has CE Mark in the European Union and United Kingdom. The GEN11 has clearance for distribution in the United States by the FDA and is CE marked in the European Union and United Kingdom. The study devices will use the cleared labeling. The Sponsor requires no additional labeling in this study.

3.3.2.5 Accountability of Study Products

The ENSEAL X1 may be provided to the participating institutions. The GEN11 (including footswitches) may be loaned to any institution in the study. Each institution not provided with ENSEAL X1 will use devices acquired through normal procurement process. If

institutions are provided ENSEAL X1, the 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 certain prior medication therapy used up to 30 days prior to surgery. These medications include aspirin, antiplatelet agents, nonsteroidal anti-inflammatory drugs, and anticoagulants. Review will occur during Visit 1 (Screening Visit) and Visit 2 (Procedure Visit).

Subjects will be assessed for occurrence of pre-surgical radiation/chemotherapy used up to 90 days prior to surgery. Review will occur during Visit 1 (Screening Visit) and Visit 2 (Procedure Visit).

Subjects may continue with their current medical care while in the study and the following medications will be collected for this study:

- Certain prior medication therapy used up to 30 days prior to surgery (listed above); and
- Any medications administered during the study due to a device-related or procedure-related AE.

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;
- Pregnancy test result, if taken as per standard of care;
- American Society of Anesthesiologists Physical Status Classification System (ASA) score;
- Occurrence and location of cancer, if applicable;
- Review and collection of relevant medical history and surgical history including the following:
    - For the gynecological procedure group, the gravidity and parity;
    - Surgical procedure to be conducted, including primary indication for surgery; and
    - Smoking history (current smoking status, if stopped, length of time [months and years]).

3.4.2 Surgical Variables

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

- Date/time of hospital admission;
- Body weight (kg or lbs; no shoes);
- Body height (cm or in; no shoes);
- Procedure duration, defined as first skin incision to final skin closure;
- Did vessel skeletonization occur (Yes/No; if Yes, describe vessel skeletonized and device used);
- Was there presence of inflamed tissue, calcified tissues/vessels, atherosclerotic tissue, fibrotic tissue, or presence of adhesions, if applicable (Yes/No; if Yes, describe the tissue along with location);
- Were adhesions removed or divided by ENSEAL X1 (Yes/No; if Yes, describe adhesions along with location and complete 5-point scale);
- Were lymphatics and tissue bundles divided by ENSEAL X1 (Yes/No; if Yes, describe lymphatics and tissue bundles along with location and complete 5-point scale);
- Was ENSEAL X1 used for grasping tissue, tissue cutting, or tissue dissection (Yes/No; if Yes, describe activity along with location and complete 5-point scale);
- Conversion to open with reason, if applicable;
- Volume of estimated intra-operative blood loss;
- Use of any other energy device (monopolar, traditional bipolar, advanced bipolar, ultrasonic) in primary procedure (type, name, and number of device and reason for use), if applicable;
- Name, product code, and number of Ethicon trocars used with ENSEAL X1, if applicable;
- Was there prophylactic use of clips as standard of surgical care before vessel transection (Yes/No; if Yes, name vessel transected, and number of clips prophylactically applied);
- For each vessel transected with ENSEAL X1:
    - Name of each vessel;
    - Hemostasis grading scale assessment;
    - Surgeon determination of diameter size range (< 3 mm, 3 to 5 mm, and > 5 to 7 mm);
    - Image captured where the vessel is perpendicular and below the open jaw of the ENSEAL X1 device;
    - For every Grade 3 vessel transection:
        - Compression used as a mild intervention, if applicable (Yes/No);
        - Touch-ups with a monopolar device, if applicable (Yes/No; if Yes, record number of touch-ups);

        - Touch-ups with a bipolar device, if applicable (Yes/No; if Yes, record number of touch-ups);
        - Touch-ups with ENSEAL X1 (Yes/No; if Yes, record number of touch-ups);
    - For every Grade 4 vessel transection intervention:
        - Type, name, and number of times used for each additional hemostatic measure used along with a description of why it was considered Grade 4;
- For the gynecological procedure group, if applicable:
    - Estimated uterine size;
- Occurrence of blood transfusion, if applicable (record the total required units of blood and rationale);
- Concomitant procedures, if applicable (defined as any medical or surgical procedure beyond activities associated with primary study procedure). If a concomitant procedure requires vessel transection by ENSEAL X1, each vessel transected will have the same information collected as stated above for vessel transections, but these will not be included as part of the primary endpoint;
- Concomitant medication usage associated with device-related or procedure-related AEs and specific drugs used up to 30 days prior to surgery (aspirin, antiplatelet agents, nonsteroidal anti-inflammatory drugs, anticoagulants) and 90 days prior to surgery (pre-surgical radiation/chemotherapy); and
- Date/time of hospital discharge.

3.4.3 Questionnaires

Data related to the following study variables will be obtained from the Task Questionnaire after every completed procedure (only for lower GI/large intestine resection and gynecological procedures), the Surgeon Questionnaire for every investigator after they have completed his/her second procedure (upper GI, lower GI, and gynecological procedures), and a GEN11 Questionnaire after every completed procedure.

Task Questionnaire

Investigators will be asked to answer a non-validated device questionnaire related to his/her experience using the ENSEAL X1 and overall assessment of how the device performed in various tasks during the procedures. The survey will be completed by the Investigators as soon as possible after each lower GI/large intestine resection and gynecological procedures, preferably on the same day. The survey responses will then be transcribed onto eCRFs.

Surgeon Questionnaire

Investigators will be asked to answer a non-validated surgeon questionnaire related to his/her experience using the ENSEAL X1. The survey will be completed by the Investigators as soon as possible after they have completed his/her second procedure in any of the six procedure groups. The survey responses will then be transcribed onto eCRFs. The questionnaire will be completed for the upper GI, lower GI, and gynecological procedures.

Generator Questionnaire

Investigators will be asked to answer a non-validated generator questionnaire related to his/her experience using the GEN11 and any ENSEAL and/or HARMONIC device. The survey will be completed by the Investigators as soon as possible after each procedure, preferably on the same day for each GEN11 used. The survey responses will then be transcribed onto eCRFs.

3.4.4 Safety Data Variables

All device-related and procedure-related AEs will be collected as outlined in Section 5.0.

3.5 SCHEDULE OF EVENTS

Table 1: Schedule of Events

Activity	Visit 1[a]	Visit 2[a]	Visit 3	Unscheduled Visit, if applicable
	Screening Visit (-56 to 0 Days)	Procedure Through Discharge Visit (Day 0)	Post Procedure Follow Up Visit (28 ± 14 Days)[b]	
Informed consent	X			
Demographics (age, gender, race, and ethnicity)	X			
Administer pregnancy test as per standard of care	X			
Height and weight (both with no shoes)		X		
Medical and surgical history (including diagnosis)	X	X		
Background information (including smoking history)	X	X		
Review of inclusion/exclusion criteria	X	X		
Concomitant medications	X	X	X	X
Surgical data collected for evaluation		X		
Collect vessel image[c]		X		
Collect task questionnaire[d]		X		
Collect generator questionnaire[e]		X		
Collect surgeon reported questionnaire[f]		X		
Concomitant procedures conducted besides primary procedure		X		
Re-operation(s) associated with the primary procedure			X	X
Assess for device-related and procedure-related AEs		X	X	X
Subject completion/discontinuation		X	X	X

a. Visit 1 and Visit 2 may be combined;
b. This can be either an office visit or telephone follow-up;
c. The image captured where the vessel is below the open jaw of the ENSEAL X1 device perpendicular to the vessel during the primary procedure at Visit 2;
d. The task questionnaire will be completed after every lower GI/large intestine resection and gynecological procedure;
e. The generator questionnaire will be completed after every procedure;
f. The surgeon questionnaire will be completed after the investigator has completed their second procedure in any of the six procedure groups;

AE = adverse events.

3.6 STUDY PROCEDURES

3.6.1 Visit 1 – Screening (may occur over visits within 8 weeks of Visit 2 including up to the day of the procedure)

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 3.4 will occur prior to the study procedure.

3.6.2 Visit 2 – Procedure Through Discharge Visit

Pre-procedure

The following must be obtained prior to the surgical procedure:

- Height and weight (both with no shoes); and
- Updates to concomitant medication and medical/surgical/smoking 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 date of surgery, subjects will have a follow-up visit approximately 28 days (± 14 days) later. 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 Unscheduled Visit(s)

Any unscheduled visit between Visit 2 and Visit 3 will be documented including the reason for the visit. This visit can be either an office visit or a telephone follow-up. Data to be collected is listed in Section 3.5.

3.6.5 Vessel Image Capture

The preferred image should be captured during the primary procedure at Visit 2 where the vessel (or the tissue bundle containing the vessel) is below the open jaw of the ENSEAL X1 device. The image should show the device perpendicular to the vessel. The image should have the entire length of the jaw of the ENSEAL X1 device in view. The image will be uploaded to the electronic database capture (EDC) system as either jpeg or pdf file. The Sponsor will determine if the image is analyzable and then each image will be reviewed and have a vessel size determined (if measurement is feasible) to the nearest quarter decimal (e.g., 5.0 mm, 5.25 mm, 5.50 mm, etc.) by the Sponsor utilizing computer software with the measurement captured in the EDC. No reconciliation will be performed between the surgeon determination of vessel size (see Section 3.4.2) and the vessel size determined by the image analysis. The primary vessel size determination will be by the surgeon determination.

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 investigation. 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 electronic database 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, 350 Hudson St. 9th Floor, NY, NY 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 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.

A 24/7/365 Help Desk Support line (telephone: 973-659-6780; fax: 973-954-5621; toll free: 866-633-4328; Email: helpdesk@mdsol.com) staffed by the outsourced vendor will also be available to respond to site and monitor questions.

4.1.3 Data Collection

Each EDC eCRF will be completed by the principal investigator or principal investigator'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 principal investigator is responsible for reviewing and approving each completed eCRF. Assurance of overall review and approval will be documented by the principal investigator 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 principal investigator must maintain all documentation related to the study until notified by the Sponsor. The principal investigator 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 and verbatim AEs captured on eCRFs will be performed using a coding thesaurus algorithm. The Medical Dictionary for Regulatory Activities (MedDRA) will be used after data entry and query resolution, via auto-encoding and interactive coding processes.

4.3 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 either onsite or offsite monitoring visits; any discrepancies will be resolved with the Investigator or designees, as appropriate.

4.3.1 Site Personnel Training

Prior to screening subjects for this study, the principal investigator, 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.

4.3.2 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.

4.3.3 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.

4.4 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. Protocol deviations will be captured in the eCRFs. The principal investigator will report protocol deviations to the IRB/EC as required by the IRB/EC 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 ENSEAL X1 device utilized for transection of a least one vessel.

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 as the collection of data for the primary and secondary performance endpoints occurs intra-operatively. The final visit occurs approximately 4 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 4-week follow-up visit, and any information entered in the eCRFs at this visit will correspond to the 4-week 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 2.4. The following hypothesis will be evaluated for the primary endpoint:

$$H_0: p \leq 87.5\%$$

$$H_1: p > 87.5\%$$

Where *p* is the percentage of transections achieving a Grade 3 or lower hemostasis rating and 87.5% is set as a performance goal for the lower bound of acceptable hemostasis. A 95% confidence interval will be calculated for *p* based on the sample proportion of transections where Grade 3 or lower hemostasis was achieved using Clopper-Pearson's method and the lower limit of this confidence interval will be compared to 87.5% to evaluate the above hypotheses. A p-value will be determined based on exact binomial test.

Given that multiple transections per subject may occur, a sensitivity analysis will be performed using appropriate methods to account for the potential correlation among the outcomes of multiple transections within the same subject and procedure. Further details of this approach will be provided in the SAP.

5.5 LEVELS OF SIGNIFICANCE

The hypotheses above will be evaluated using a one-sided significance level of 0.025. 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 ENSEAL X1 device is utilized during the surgical procedure. The summary of all performance and safety endpoints will be performed by procedure group and procedure subgroup on the entire pooled set of subjects. The hypotheses described in Section 5.4 will be evaluated on the pooled set of subjects as data on the ENSEAL X1 Large Jaw device demonstrated consistent performance across procedure groups in a similar study (>94% Grade 3 or lower hemostasis achieved for each procedure group).

5.7 SAMPLE SIZE JUSTIFICATION

A sample size of at least 230 vessel transections is required to have a minimum of 90% power for rejecting the null hypothesis when the expected rate of Grade 3 hemostatic transections is at least 94.0% based on exact binomial test and a one-sided significance level of 0.025. The hemostatic transection grades for vessels are assumed to be independent within a subject and procedure.

In order to achieve a total of 230 vessel transections for analysis with a minimum of 27 vessel transections in each group (including 4 subgroups in upper GI procedure), a minimum of 133 subjects (a maximum of 149 subjects) will be enrolled in the study.

The original sample size of the study was based on the assumption of one vessel transection per subject. At the time of amendment 5 the number of transections per subject was estimated to be 1.9 on average. The primary endpoint and the study hypothesis are based on hemostasis of vessel transection; therefore, the number of subject to be enrolled was updated to ensure 230 vessel transections.

Given that the primary endpoint is being evaluated intra-operatively, it is not anticipated that there will be subject dropout prior to evaluating this endpoint, thus no adjustment or increase in subject enrollment is planned to account for dropout. A minimum of 27 vessel transections in each group (including 4 subgroups in upper GI procedure) is planned to attain optimum representation of each of the procedure groups to the whole study sample.

From a safety perspective on the pooled analysis of 133 subjects and in consideration of rare AEs that may occur (e.g., bleeding requiring blood product transfusion), for an event that has an incidence rate of, for example, 1%, then in a sample of 133 subjects, the probability of observing at least 1 event is 73.7% under a binomial probability model. Thus, this sample size provides a high probability of observing rare events if they do occur, and provides reasonable assurance to conclude that the likelihood of such AEs is less than 2.8% if they do

not occur based on the upper limit of an exact 95% confidence interval when 0 events out of 133 subjects are observed.

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 and procedure subgroups 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, and race) will be presented in total and by procedure group and procedure subgroups. Surgical characteristics including, at minimum, estimated blood loss, requirement for blood transfusion, and procedure duration will be summarized by procedure group, procedure subgroup and in total.

5.9.4 Primary and Secondary Endpoint Analyses

The number and percentage of vessels where hemostasis is achieved (≤ Grade 3) will be summarized and an exact 95% confidence interval will be estimated for each procedure group, procedure subgroup, and in total based on Clopper-Pearson's method. The performance goal hypothesis will be tested as described in Section 5.4.

The analysis of primary endpoint is based on the assumption of independence of hemostatic grades within subject and procedure. This assumption of independence and its impact on the overall study conclusion will be evaluated through sensitivity analyses and will be described in SAP.

Counts and percentages will be provided for type, size, and number of vessels transected, as well as for the grading scale distribution for all vessels transected, number of times ENSEAL X1 touch-ups were required, incidence of requirement for additional measures to obtain hemostasis on vessels (other advanced energy devices or hemostatic measures), and 5-point scale scores for various tasks completed by the ENSEAL X1 device (adhesiolysis, lymphatics or tissue bundles divided, tissue grasping, tissue cutting, or tissue dissection).

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, procedure subgroup, and in total. Separate summaries will be provided for device-related and procedure-related AEs. Serious AEs will be summarized in a similar manner.

5.9.5 Plans for Interim Analyses

No interim analyses are planned for this study.

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.

5.9.7 Subgroup Analyses

Subgroup analyses are planned to be performed for the subgroup of subjects who have a medical history of treatment for cancer (e.g. chemotherapy or radiation) and 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

Only AEs considered 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 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;
- 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.

6.1.3 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:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **MODERATE:** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **SEVERE**: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

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 possibly, probably, or causally related to the study procedures or the ENSEAL X1 or GEN11 devices 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.
- **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;
        - 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 ENSEAL X1 or GEN11 devices 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 study devices;
- 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 2 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 SAEs to the reviewing IRB/EC per their IRB/EC 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 investigation. Product complaints related to an Ethicon-manufactured ENSEAL X1 or GEN11 devices 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. The Product Complaint Form must be emailed to the Sponsor Customer Complaint team at the following email address:

Productcomplaint1@its.jnj.com

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.

7.1.2 Reporting of Approved Marketed Devices and Commercially Available Devices (not Ethicon)

The site should report Product Complaints of non-Ethicon devices that are approved marketed devices or commercially available medical devices according to the specific product's manufacturer specifications/guidelines.

8.0 REFERENCES

1. Siegel JM, Cummings JF, Clymer JW. Reproducible, repeatable and clinically-relevant hemostasis scoring. J Adv Med Pharm Sci 2014;1:30-39.