MDT17025SIG

A prospective, two-arm, multicenter, post market study to confirm the safety and performance of the Signia™ Stapling System using Endo GIA™ Reloads with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads in abdominal and thoracic procedures.

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Study Protocol, 10-AUG-2018

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Clinical Investigation Plan

Clinical Investigation Plan/Study Title	A prospective, two-arm, multicenter, post market study to confirm the safety and performance of the Signia™ Stapling System using Endo GIA™ Reloads with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads in abdominal and thoracic procedures.
Clinical Investigation Plan Identifier	MDT17025SIG
Study Product Name	Signia™ Stapling System using Endo GIA™ Reloads with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads
Sponsor/Local Sponsor	Sponsor: Covidien-Medtronic Minimally Invasive Therapies Group Surgical Innovations 15 Hampshire St. Mansfield MA 02048 Local Sponsor: Covidien Services Europe (an indirect, wholly owned subsidiary of Medtronic plc.) Medtronic PLC, Block 3090-3094, Lake Drive, Citywest Business Campus, Co. Dublin, D24 XN47, Ireland
Document Version	3.0, 10-Aug-2018

Confidentiality Statement

1. Investigator Statement

Study product Name	Signia™ Stapling System using Endo GIA™ Reloads with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads
Sponsor	Sponsor: Covidien-Medtronic Minimally Invasive Therapies Group Surgical Innovations 15 Hampshire St. Mansfield MA 02048 Local Sponsor: Covidien Services Europe (an indirect, wholly owned subsidiary of Medtronic plc.) Medtronic PLC, Block 3090-3094, Lake Drive, Citywest Business Campus, Co. Dublin, D24 XN47, Ireland
Clinical Investigation Plan Identifier	MDT17025SIG
Version Number/Date	3.0, 10-Aug-2018
I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to comply with United Stated Food and Drug Administration (USA) or ISO 14155:2011 (EU) regulations under which the study is being conducted. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.	
Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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2. Glossary

Term	Definition
ADE	Adverse device effect - Adverse event related to the use of an investigational medical device. Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation or any malfunction of the investigational medical device. Note: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. See Clinical Event definition for more information.
AE	Adverse event - Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. Note: This definition includes events related to the investigational medical device or the comparator. Note: This definition includes events related to the procedures involved. Note: for users or other persons, this definition is restricted to events related to investigational medical devices. See Clinical Event definition for more information.
ASA	American Society of Anesthesiologists
BMI	Body mass index (kg/m^2) - BMI is a person's weight in kilograms (kg) divided by his or her height in meters squared.
CC	Cubic centimeter (liquid volume)
CIP	Clinical Investigation Plan (can be used synonymously with Protocol)

Term	Definition
COPD	Chronic obstructive pulmonary disease - a chronic condition in which there is a slow, progressive obstruction of airflow into or out of the lungs
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Note: Device deficiencies include malfunctions, use errors, and inadequate labeling. See Clinical Event definition for more information.
eCRF	Electronic Case Report Form
ICJME	International Committee of Medical Journal Editors
IFU	Instructions for use
ISO	International Organization for Standardization
ITT	Intent-to-treat
LCD	Liquid crystal display
LED	Light emitting diode
LRYGB	Laparoscopic Roux-en-Y gastric bypass – A type of weight loss surgery that reduces the size of the upper stomach to a small pouch by stapling off the upper section of the stomach then attaches this pouch directly to part of the small intestine called the Roux limb forming a “Y” shape.
LSG	Laparoscopic sleeve gastrectomy – A laparoscopic surgical weight-loss procedure in which the stomach is reduced, by surgical removal of a large portion of the stomach along the greater curvature resulting in a sleeve or tube-like structure
MedDRA	Medical Dictionary for Regulatory Activities

Term	Definition
OLED	Organic light emitting diodes
RDC	Remote data capture
SAE	Serious Adverse Event - Adverse event that: a. Led to a death, b. Led to a serious deterioration in the health of the subject, that either resulted in: 1. Resulted in a life threatening illness or injury, or 2. Resulted in a permanent impairment of a body structure or a body function, or 3. In-patient or prolonged hospitalization, or 4. Medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or c. Led to fetal distress, fetal death or a congenital abnormality or birth defect. Note: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
SADE	Serious Adverse Device Effect - Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
USADE	Unanticipated Serious Adverse Device Effect - Any serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. Note: Anticipated serious adverse device effect (ASADE) is an effect which by nature, incidence, severity or outcome has been identified in the risk analysis report.
VATS	Video assisted thoracic surgery

3. Synopsis

Title	A prospective, two-arm, multicenter, post market study to confirm the safety and performance of the Signia™ Stapling System using Endo GIA™ Reloads with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads in abdominal and thoracic procedures.
Clinical Study Type	Post-market, prospective, two-arm, multi-center
Product Name	Signia™ Stapling System using Endo GIA™ Reloads with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads
Sponsor	Covidien-Medtronic Minimally Invasive Therapies Group Surgical Innovations 15 Hampshire St. Mansfield MA 02048
Local Sponsor	Covidien Services Europe (an indirect, wholly owned subsidiary of Medtronic plc.) Medtronic PLC, Block 3090-3094, Lake Drive, Citywest Business Campus, Co. Dublin, D24 XN47, Ireland
Indication under investigation	Abdominal and thoracic procedures for resection, transection and creation of anastomosis per the instructions for use (IFU)
Product Status	**Signia™ Stapling System** • Food and Drug Administration (FDA) 510K cleared (USA) • CE Mark approval (EU), Self-Declared
Primary Objective(s)	The objectives of this prospective, two-arm, multicenter post-market study is to confirm safety and performance through the incidence of subjects reporting serious adverse device effects (ADEs) up to and including 30 (+14) days following use of Signia™ Stapling System with Endo GIA™ with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads in subjects undergoing indicated abdominal or thoracic procedures for resection, transection and creation of anastomosis per the IFU.
Secondary Objective(s)	The secondary endpoint is device deficiency/malfunctions affecting the intended performance of the device to include;

	• Staple line assessment:
	  ○ Intraoperative assessments:
	  ▪ Assessment of staple line integrity
	  ▪ Incidence of staple line bleeding (measured as ≥ 50 cc)
	  ▪ Additional intervention(s) to treat staple-line failure (ex: glue, manual over sew, Medtronic buttress) or intraoperative revision/recreation of the anastomosis
	  ▪ Incidence of leakage (as measured by air leak test, or standard of care, as applicable)
	  ○ Post-operative assessments:
	  ▪ Duration of air leakage (in days) for thoracic procedures
	  • Prolonged air leaks are considered >7 days
	  ▪ Incidence of leakage for abdominal procedures as evidenced confirmed by imaging, subject presentation or decline in status, or need for reoperation/re-intervention
	  ▪ Incidence of post-operative infection assessed by the Investigator according to the standard of care and site policy, ex. Positive wound culture
	  ▪ Additional intervention(s) to treat staple-line failure
	• Incidence of repeat hospital admissions for primary procedure-related complications.
	
	All recorded device deficiencies/malfunctions will be captured and assessed by the Investigator. Complaints will be handled in accordance with the standard procedures for the post-market vigilance system.

Randomization	There will be no randomization used for this study
Sample Size	A minimum of 127 subjects will be enrolled under 2 study arms, (abdominal or thoracic) at approximately 10 sites in the USA and Europe (potentially in United Kingdom, Spain, Italy). • Abdominal (approximately 53 subjects) • Thoracic (approximately 74 subjects)
Inclusion/Exclusion Criteria	Inclusion Criteria

	1. Adults (male or female) between 22 and 80 years of age inclusive at the time of the procedure. 2. The subject must be willing and able to participate in the study procedures and to understand and sign the informed consent. 3. The subject is scheduled to undergo an indicated primary abdominal or thoracic procedure for resection, transection and creation of anastomosis per the IFU where the Signia™ Stapling System with Endo GIA™ with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads will be used per its IFU. Additionally, if considered appropriate for the procedure only Medtronic buttresses can be used during the course of the study. a. Thoracic procedures may include, but are not limited to wedge resection and lobectomy, and may include video assisted thoracic surgery (VATS) or open procedures b. Abdominal procedures may include, but are not limited to, laparoscopic sleeve gastrectomy (LSG), laparoscopic Roux-en-Y gastric bypass (LRYGB) Exclusion Criteria 1. Subjects undergoing cardiac and vascular procedures 2. The procedure is an emergency procedure 3. The procedure is a revision/reoperation of a primary operation 4. Any female subject who is pregnant a. Females of child-bearing potential will be required to undergo either a urine pregnancy test or serum pregnancy test during Screening and confirmed on the day of operation (except for subjects who are surgically sterile or are post-menopausal for at least two years) (USA only) and per EU local requirements 5. Any subject who is considered to be part of a vulnerable population (e.g. prisoners or those without sufficient mental capacity) 6. The subject is unable or unwilling to comply with the study requirements or follow-up schedule 7. The subject has comorbidities which, in the clinical judgment of the Investigator, will not be appropriate for the study or the subject has an estimated life expectancy of less than 6 months 8. The subject has been diagnosed with a bleeding disorder and/or is undergoing active and not reversed anticoagulant treatment.

	9. The subject is concurrently enrolled in another investigational drug or device research study or has been enrolled in another study within 30 days of enrollment. 10. Pre-existing/chronic conditions specific to Tri-Staple™ 2.0 Reload contraindications as described in the IFU.
Study Procedures and Assessments	Subjects will be evaluated at screening, day of operative visit, discharge, and 30 (+14) days post-operative. Assessments to be conducted/data collected include: **Screening:** • Eligibility Criteria • Subject demographics (e.g., sex, age, ethnicity and race if allowed per local regulations) • Medical and surgical history (previous abdominal or thoracic surgical history, smoking history, anticoagulant therapies and prevalence of diabetes) • Vital signs (heart rate, temperature, respiratory rate, blood pressure) • Oxygen saturation levels • BMI • Abbreviated physical exam, including height, weight, and examination of the heart, lung, and abdomen • Serum or urine pregnancy test females of child bearing potential (USA only) or per EU local requirements **Operative Visit:**

	• Eligibility Criteria*
	• Vital signs (heart rate, temperature, respiratory rate, blood pressure, pulse, oxygen saturation levels)*
	• Abbreviated physical exam, including height, weight, and examination of the heart, lung, and abdomen*
	• American Society of Anesthesiologists (ASA) grade (See Appendix B, Section 18.2)
	• Serum or urine pregnancy test females of child bearing potential (USA only) or per EU local requirements *
	* Assessments only need to be repeated if Screening/Operative Visit occur on different days
	• Operative date
	• Operative start (skin incision) and stop times (skin closure)
	• Type of procedure
	• General anesthesia information (type, start and stop times)
	• Study device data (i.e., type of reload used, staple size, lot number of devices used, number of firings, location of firings)
	• Use of Signia feedback display during surgery (if applicable)
	• Relevant concomitant medications (only those related to relevant medical history or adverse events will be collected e.g.: anticoagulants, blood pressure, antibiotics, pain medications)
	• Procedure related adverse events and adverse device effects (ADEs)
	• Staple line assessment
	• Device deficiencies/malfunctions affecting intended performance to include but not limited to;
	  ○ System set-up (insertion guide, power shell)
	  ○ Organic light emitting diode (OLED) screen display
	  ○ Rotation
	  ○ Articulation
	  ○ Clamp/UnClamp
	  ○ Firing
	  ○ Use of manual retraction tool
	  ○ User errors
	  ○ Unintended cutting
	  ○ Insufficient staple deployment
	  ○ Inability to complete the firing sequence
	  ○ Stapling without cutting
	• Device accountability
	
	Discharge Assessments:
	• Procedure related adverse events and adverse device effects

	• Length of hospital stay • Length of intensive care unit stay (if applicable) • Surgical site and infection assessment by the Investigator according to the standard of care and site policy, ex. Positive wound culture • Relevant concomitant medications (only those related to relevant medical history or adverse events will be collected e.g.: anticoagulants, blood pressure, antibiotics, pain medications) **Follow-up Assessments (Post-operative day 30 (+14)):** • Readmission related to primary procedure • Procedure related adverse events • Adverse device effects (ADEs) • Surgical site and infection assessment by the Investigator according to their the standard of care and site policy, ex. Positive wound culture • Relevant concomitant medications (only those related to relevant medical history or adverse events will be collected e.g.: anticoagulants, blood pressure, antibiotics, pain medications)
Statistics	**Sample Size Determination** Sample size was determined based on the primary endpoint (incidence of subjects reporting serious adverse device effects up to and including 30 days(+14 days) post-procedure) and considering an acceptable probability (≥ 80%) to observe at least one adverse device effect within 30 days, in each arm (abdominal or thoracic indication). A previous Medtronic study (ClinicalTrials.gov ID NCT02500537) conducted on N=100 subjects and evaluating an equivalent device (Endo GIA™ Reinforced Reload with Tri-Staple™ Technology) in the same indications and with a similar design and follow-up reported the following adverse device effect rates (described as “device related adverse events” with the study protocol and final report): Abdominal: Adverse device effect incidence 3.3%; Thoracic: 2.5% Because of the expected low adverse device effect incidence rate (<5%) in the Abdominal or Thoracic procedures, as described above, a

	Poisson distribution is applied to estimate the probability of observing AE event(s). In the Abdominal indication, for an anticipated sample size of 53 subjects using an adverse device effect rate of 3.3%, and including a 5% attrition rate within 30 days, we obtain a probability of 81% to observe at least 1 adverse device effect. In the Thoracic indication, for an anticipated sample size of 74 subjects using an adverse device effect rate of 2.5%, and including a 5% attrition rate within 30 days, we obtain a probability of 83% to observe at least 1 adverse device effect. For the overall population (in both indications), with a sample size of 127 subjects considering an averaged adverse device effect rate of 2.9% and an attrition rate of 5% within 30 days, we obtain a probability of 97% to observe at least 1 adverse device effect, and a probability of 86% to observe at least 2 adverse device effects. In any scenario, we will have ≥ 80% probability to observe at least 1 adverse device effect in each arm. **Primary Endpoint Analysis** The primary endpoint is the incidence of subjects reporting serious adverse device effects up to and including 30 days (+14 days) postop. It will be summarized using descriptive statistics. A two-sided 95% confidence interval will also be calculated. The acceptance criteria for this endpoint is an upper limit of the 95% CI below 20%. The analysis will be performed in abdominal group and in thoracic group, and in the combined groups. **Secondary Endpoint Analysis** The incidence of secondary outcome measures will be summarized using descriptive statistics: • counts and percentages for categorical data mean, standard deviation, median, minimum and maximum for quantitative data.

Interim Analysis	A preliminary analysis will be conducted in the study when a total of 64 subjects have been enrolled and completed the 30 day follow up visits.

4. Introduction

4.1. Background

During abdominal and thoracic procedures, staple line failure can result in severe intraoperative and postoperative complications. After thoracic lung resection, postoperative air leaks are the most common complication with a reported occurrence between 4% and 58% [1-5]. In patients with concomitant chronic obstructive pulmonary disease (COPD) and fused fissures these rates can climb as high as 90% [6]. Thoracic air leak complications can include reduced mobility, increased hospital stay, the need for longer chest tube time (often associated with increased pain), and risk of further complications [1].

With the exception of staple lines across a distal obstruction or severe ileus, leaks are less common during gastrointestinal surgery due to lower intraluminal pressures to which the staple lines are exposed. If leaks do occur; however, the complications can be severe. Postoperative leak rates following laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB) have been reported between 1% and 3% and leak-associated mortality has been reported at 0.1% [7-11].

Clearly, the integrity of the staple line is a primary factor in the creation of a stable anastomosis. The various characteristics of each tissue type present unique challenges and until now the firing speed used during these procedures was determined by the surgeon, particularly when using a manual firing setup [12]. Ultimately relying on generation of the ideal ‘B’ shaped staples, surgeon experience played a crucial role in effective staple line production [13, 12].

The Signia™ Stapling System with Endo GIA™ with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads uses a single-use reload. Automatically adjusting firing speed to optimize staple formation using an onboard intelligence, the Signia™ Stapling System generates consistent staple lines and real-time surgeon feedback via an OLED display. Additionally, the Signia™ Stapling System can be used single handed. To date single-handed use has proved challenging for many surgeons using manual firing systems.

4.2. Purpose

The purpose of this study is to confirm the safety and performance of the Signia™ Stapling System with Endo GIA™ with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads in a minimum of 127 enrolled subjects undergoing indicated abdominal or thoracic procedures enrolled at approximately 10

sites in the USA and Europe (potentially in the United Kingdom, Spain, Italy). At the conclusion of the study, data will be submitted for publication.

5. Objectives and Endpoints

5.1. Objectives

The objective of this prospective, two-arm, multicenter post-market study is to confirm safety and performance through the incidence of subjects reporting serious adverse device effects (ADEs, as defined by ISO14155:2011, see section 11.1.3 for additional details) up to and including 30 (+14) days following use of Signia™ Stapling System with Endo GIA™ with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads in subjects undergoing indicated abdominal or thoracic procedures. (See Section 18.1 Appendix A, for Reloads to be assessed in this study)

5.1.1. Primary Objective(s)

The primary endpoint is the incidence of subjects reporting serious adverse device effects (ADEs) up to and including the 30 day (+14 day) post-operative follow up visit including intra- and post-operative leaks. The causes of these leaks will be documented when available.

5.1.2. Secondary Objective(s)

The secondary endpoint is device deficiency/malfunction affecting the intended performance of the device to include;

- Staple line assessment:
    - Intraoperative assessments:
        - Assessment of staple line integrity
        - Incidence of staple line bleeding (measured as ≥ 50 cc)
        - Additional intervention(s) to treat staple-line failure (ex: glue, manual over sew, Medtronic buttress) or intraoperative revision/recreation of the anastomosis
        - Incidence of leakage (as measured by air leak test, or standard of care, as applicable)
    - Post-operative assessments:
        - Duration of air leakage (in days) for thoracic procedures
            - Prolonged air leaks are considered >7 days
        - Incidence of leakage for abdominal procedures as evidenced confirmed by imaging subject presentation or decline in status, or need for reoperation/re-intervention
        - Incidence of post-operative infection, assessed by the Investigator according to the standard of care and site policy, ex. positive wound culture
        - Additional intervention(s) to treat staple-line failure
- Incidence of repeat hospital admissions for primary procedure-related complications.

All recorded device deficiencies/malfunctions will be captured and assessed by the Investigator. Complaints will be handled in accordance with the standard procedures for the post-market vigilance system.

6. Study Design

The purpose of this study is to confirm the safety and performance of the Signia™ Stapling System with Endo GIA™ with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads in a minimum of 127 enrolled subjects undergoing indicated abdominal or thoracic procedures enrolled at approximately 10 sites in the USA and Europe (potentially in the United Kingdom, Spain, Italy).

6.1. Duration

Including enrollment/screening and follow-up time for all enrolled subjects the study is estimated to progress for up to 24 months. Not including hospital stay (which could vary depending on the procedure), subjects will participate for potentially 74 days. Screening for eligibility may occur 30 days (inclusive) prior to the procedure. Post-procedure, subjects will be assessed for incidence of adverse device effect events up to and including the 30 day (+14 day) post-operative follow up visit.

6.2. Rationale

In order to assess the clinical safety of the Signia™ Stapling with Endo GIA™ with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads, Medtronic is performing a prospective, two-arm, multicenter, post-market study on adult subjects undergoing abdominal or thoracic procedures using the device and appropriate Reloads (See Appendix A). During the procedure device deficiencies affecting the intended performance of the device will be collected and incidence of reported adverse device effects will be assessed up to and including the 30 day (+14 day) post-operative follow up visit following the procedure. This study does not utilize any randomization or blinding. Currently there are no known factors that may compromise study outcomes or the interpretation of results (e.g., baseline characteristics, concomitant medications, the use of other study products, or subject-related factors such as age, gender or lifestyle). If any adverse device effect occurrences are identified they will be assessed, reported and documented in the eCRF.

6.3. Selection of Investigators

Surgeons who are qualified by training (board certified in abdominal and/or thoracic procedures in accordance with USA/European and hospital guidelines), education, and relevant experience appropriate to the use of the product and associated procedures will be considered for participation as investigators in this study. Investigators/sites must have adequate time and resources to conduct the study throughout the duration of the study and have access to an adequate number of eligible subjects. Investigators/sites must be able to comply with applicable Institutional Review Board (IRB)/Ethics Committee (EC) and regulatory requirements. Investigator must not be debarred, disqualified, or working under sanctions in applicable regions. Qualifications are verified through valid Curriculum Vitae (CV) and current licensing. Current license (USA only) and CVs will be maintained with study documentation.

The Investigators and the associated clinical study staff will receive training on the management of the clinical study and the device according to the instructions for use (IFU).

7. Product Description

7.1. General

The Signia™ stapler is a reusable intelligent surgical stapler that provides push-button powered maneuverability and delivery of compatible stapling reloads. The Signia™ Stapling System is the combination of the Signia™ stapler and system accessories.

The Signia™ stapler is composed of the Signia™ power handle, Signia™ power shell, and Signia™ adapters. The system accessories include a reusable insertion guide, a manual retraction tool, a single-bay charger. The Signia™ stapler is compatible with Endo GIA™ single-use reloads, Endo GIA™

single-use reloads with Tri-Staple™ Technology, Tri-Staple™ 2.0 single-use reloads, and Signia™ Intelligent Loading Units with Tri-Staple™ 2.0 single-use Reloads (see appendix A for Reloads to be assessed in this study).

7.1.1. Signia™ Stapler

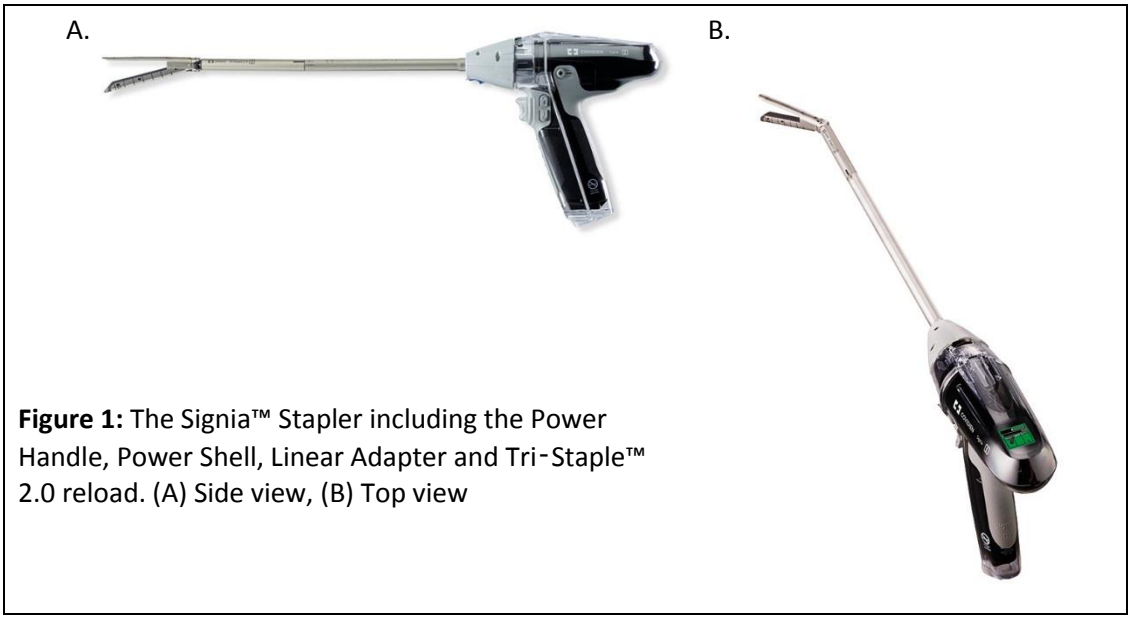

Figure 1: The Signia™ Stapler including the Power Handle, Power Shell, Linear Adapter and Tri-Staple™ 2.0 reload. (A) Side view, (B) Top view

7.1.1.1. Signia™ Power Handle

The Signia™ power handle is a non-sterile reusable, battery-powered stapling handle that includes microprocessors, electronics, motors, an OLED display screen, and a rechargeable lithium (Li)-ion battery.

The Power Handle provides instrument intelligence (software) and contains a microprocessor, that controls supporting electronics, and motor assemblies for rotation, articulation, jaw open/close and firing of compatible stapling reloads. The control of the reloads is provided by three motor assemblies in the handle, and then delivered to the attached Linear Adapter through multiple drive shafts to deploy the compatible reloads.

The “Intelligence Enabled” symbol is a trademarked symbol originated by Medtronic that is used in the branding of Signia™ Stapling products. It means that the product contains an ID-enabled IC chip. The chip will have the ability to communicate with compatible Signia™ stapling products that also have an ID-enabled IC chip.

7.1.1.2. Signia™ Power Shell

The Signia™ power shell is a single-use, sterile shell that covers the non-sterile Signia™ power handle to create an aseptic barrier, control interface, and universal adapter connector. It also provides a communications interface for Tri-Staple™ 2.0 single-use reloads and Signia™ Intelligent Loading Units with Tri-Staple™ 2.0 single-use Reloads indicated for use with the Signia™ stapler.

7.1.1.3. Signia™ Linear Adapter(s)

The Signia™ linear adapters (short, standard and XL) are non-sterile reusable instruments that attach to the stapling handle to enable functionality of compatible stapling reloads. Included are motor mating connectors, electronic sensors, and communications interfaces for Tri-Staple™ 2.0 single-use reloads and Signia™ Intelligent Loading Units with Tri-Staple™ 2.0 single-use Reloads indicated for use with the Signia™ stapler. It is provided non-sterile and must be cleaned and sterilized prior to each use as per the instructions for use.

7.1.2. Signia™ Accessories

7.1.2.1. Signia™ Reusable Insertion Guide

The Signia™ reusable insertion guide is used to help maintain the sterility of the power shell during insertion of a non-sterile Signia™ power handle. It is provided non-sterile and must be cleaned and sterilized prior to each use as per the instructions for use.

7.1.2.2. Signia™ Manual Retraction Tool

The Signia™ manual retraction tool is a reusable, handheld device that can be used to operate the adapter controls in the event of a malfunction during operation. The tool can be used to complete a firing, retract the knife and open the jaws, and/or articulate a stapling reload. It is provided non-sterile and must be cleaned and sterilized before use as per the instructions for use.

7.1.2.3. Signia™ Single-Bay Charger

The Signia™ single-bay charger is designed for use as an accessory to the Signia™ stapler and is used for charging the Li-ion batteries within the power handle. The charger will monitor the state of charge of a charging battery and report its status using color LEDs.

7.1.3. Number of Devices to be Used

The estimated quantity of each device to be used for this study is included below. Each site will receive approximately 2 Power Handles, Single-Bay Chargers and Power Cords along with sufficient Signia™ accessories and accommodate the number of anticipated procedures.

Device	Estimated number to be used in study.
Signia ™ Power Handle	30
Signia™ Power Shell	130
Signia™ Linear Adapter (stnd, XL, short)	90
Signia™ Reusable Insertion Guide	30
Signia™ Manual Retraction Tool	30
Signia™ Single-Bay Charger	30
Signia™ Power Cord	30

7.2. Manufacturer

The Signia™ Stapling System is manufactured by Covidien LP. (Covidien LP is an indirect wholly owned subsidiary of Medtronic plc.).

7.3. Packaging

The Signia™ Power Handle and Signia™ Single-Bay Charger are packaged as non-sterile reusable instruments.

The Signia™ Power Shell is packaged as a single use, sterile shell for the Signia™ power handle.

The Signia™ Linear Adapter, Signia™ Reusable Insertion Guide, and Signia™ Manual Retraction Tool are packaged as non-sterile instruments and must be cleaned and sterilized prior to each use per IFU instructions.

7.4. Intended Population

The intended population for this study are subjects scheduled to undergo an indicated primary abdominal or thoracic procedure where the Signia™ Stapling System will be used per its instructions for use (IFU).

7.4.1. Indications for Use

The Signia™ stapler, when used with Endo GIA™ single-use reloads, Endo GIA™ single-use reloads with Tri‑Staple™ Technology, Tri‑Staple™ 2.0 single-use reloads and Signia™ Intelligent Loading Units with Tri‑Staple™ 2.0 single-use Reloads, has applications in abdominal, gynecological, pediatric, and thoracic surgery for resection, transection, and creation of anastomosis. It may be used for transection and resection of liver substance, hepatic vasculature, and biliary structures and for transection and resection of the pancreas.

The Signia™ stapler, when used with Endo GIA™ curved tip single use reloads or Tri‑Staple™ 2.0 curved tip single-use reloads, can be used to blunt dissect or separate target tissue from other certain tissue.

The Signia™ stapler, when used with Endo GIA™ single use Radial Reloads with Tri‑Staple™ Technology, has applications in open or minimally invasive general abdominal, gynecologic, pediatric and thoracic surgery for resection and transection of tissue and creation of anastomosis, as well as application deep in the pelvis, i.e., low anterior resection. It may be used for transection and resection of liver substance, hepatic vasculature and biliary structures and for transection and resection of the pancreas.

The Signia™ stapler, when used with Endo GIA™ single use reinforced reloads with Tri‑Staple™ Technology preloaded with polyglycolic acid staple line reinforcement or Tri‑Staple™ 2.0 single use reinforced reloads preloaded with polyglycolic acid staple line reinforcement, has applications in abdominal, gynecologic, pediatric and thoracic surgery for resection, transection of tissue and creation of anastomosis. It may be used for transection and resection of liver substance, hepatic vasculature and biliary structures, and for transection and resection of the pancreas.

7.4.2. Contraindications

1. Refer to the Instructions for Use provided with the compatible Endo GIA™ single-use reloads, Endo GIA™ single-use reloads with Tri-Staple™ Technology, Tri-Staple™ 2.0 single-use reloads, and Signia™ Intelligent Loading Units with Tri-Staple™ 2.0 single-use Reloads for specific indications, contraindications, warnings, and precautions.
2. Tissue thickness should be carefully evaluated before firing any stapler. Refer to the Instructions for Use provided with the selected Endo GIA™ single-use reload, Endo GIA™ single-use reload with Tri-Staple™ Technology, Tri-Staple™ 2.0 single-use reload or Signia™ loading unit with Tri-Staple™ 2.0 single-use cartridge for the specific contraindications regarding compressed tissue thickness for the selected reload.
3. Do not use the Signia™ stapler where adequacy of hemostasis cannot be verified visually after applications.
4. Do not use any linear cutter on major vessels without making provisions for proximal and distal control.
5. Do not use the instrument on ischemic or necrotic tissue.

6. The Signia™ stapler should not be used on friable or delicate tissue where the closure of the device might be destructive.
7. When using curved-tip reloads with the Signia™ stapler, do not use on tissue or structures that cannot fit completely within the reload jaws proximal to the transitional angle of the curved tip.
8. The Signia™ power shell is provided STERILE and is intended for use in a SINGLE procedure only. DISCARD AFTER USE. DO NOT RESTERILIZE.
9. Endo GIA™ single-use reloads, Endo GIA™ single-use reloads with Tri-Staple™ Technology, Tri-Staple™ 2.0 single-use reloads and Signia™ Intelligent Loading Units with Tri-Staple™ 2.0 single-use Reloads are provided STERILE and are intended for use in a SINGLE procedure only. DISCARD AFTER USE. DO NOT RESTERILIZE.

7.5. Equipment

7.5.1. Endo GIA™ with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads (single-use)

The Endo GIA™ with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads place staggered rows of titanium staples and simultaneously divides the tissue so that three staggered rows of staples are placed on either side of the cut line. The size of the staples is determined by the selection of the cartridge.

Endo GIA™ with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads are manufactured by Covidien LP. (Covidien LP is an indirect wholly owned subsidiary of Medtronic plc.). See Section 18.1 Appendix A for Endo GIA™ with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads to be assessed in this study. Details for product use are described in the instructions for use that accompany each reload.

7.6. Product Use

Details for product use are described in the instructions for use and manuals for the Signia™ Stapling System.

7.7. Product Training Requirements

Each Investigator participating in the clinical study and the associated clinical study staff will receive training on the clinical protocol, as well as the Signia™ Stapling System. Investigators and study staff will be trained on device characteristics, shelf life and storage requirements, device use, and warnings, precautions, contraindications.

7.8. Product Receipt and Tracking

Signia™ Stapling Systems and accessories will be shipped to each site and each site will document the quantity and lot number of each component (See section 7.1) upon receipt. For each procedure the serial number of each component of the device being used will be recorded in the device accountability log.

7.9. Product Storage

The Signia™ Stapling Systems will be labeled "Exclusively for Clinical Investigations" or similar language and should be stored in a secure (locked) area under the appropriate storage conditions (room temperature). Access should be limited to designated study staff only.

7.10. Product Return

It is the site's responsibility to return the Signia™ Stapling System(s) and all associated Signia™ accessories to Medtronic within 30 days of the last patient enrolled at the site.

7.11. Product Accountability

Signia™ Stapling Systems will be provided to each site upon Sponsor collection and approval of all required regulatory documentation. The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include:

- the date of receipt,
- identification of each investigational device (batch number/serial number or unique code),
- the expiry date, if applicable,
- the date or dates of use,
- subject identification,
- date on which the investigational device was returned/explanted from subject, if applicable, and
- the date of return of unused, expired or malfunctioning investigational devices, if applicable.

Device accountability will be tracked on a separate log and kept in the site binder. It is the site's responsibility to document the receipt (maintain shipping logs), disposition of the product (per subject use, including amount used, amount remaining, etc.), transfer (if applicable) and return of all unopened study devices. The sponsor shall also keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal.

8. Selection of Subjects

8.1. Study Population

A minimum of one-hundred twenty (127) subjects ages 22-80 inclusive at the time of the procedure enrolled in 2 study arms (abdominal or thoracic) at approximately 10 sites in USA and Europe (potentially in United Kingdom, Spain, Italy). See Statistics (Section 13.2) for additional details on sample size determination. It is estimated that the abdominal arm will comprise 53 subjects and the thoracic arms comprise 74 subjects.

8.2. Subject Enrollment

After being informed of the nature of the study, the subject will provide written informed consent that has been approved by the sponsor and the appropriate IRB/EC of the respective clinical site (see section 9.6 for additional details). A minimum of 127 subjects will be enrolled in the study at approximately 10 sites in the USA and Europe (potentially in United Kingdom, Spain, Italy) during competitive enrollment not to exceed 15 subjects per site. Subjects' participation in the study will last approximately 30 days (+14 days) post procedure. During the study, enrollment will continue until 127 subjects have enrolled. Once enrolled, patients will be included unless deemed necessary by the inclusion and exclusion criteria below.

A subject is considered enrolled in the study when it is confirmed they meet inclusion and exclusion criteria and ICF is signed and must be followed for the full 30 days if the procedure was begun or completed with the study device. The time of enrollment to procedure should not exceed 30 days. If enrollment and/or ICF signature occur more than 30 days before the procedure the subject is to be rescreened and reconsented. No study procedures will be performed until informed consent form has been completed.

The procedure will be performed per the institution's standard practice. Subjects will be considered for enrollment into the study if they meet specific screening inclusion/exclusion criteria. The criteria for enrollment must be followed explicitly.

8.3. Inclusion Criteria

1. Adults (male or female) between 22 and 80 years of age inclusive at the time of the procedure.
2. The subject must be willing and able to participate in the study procedures and understand and sign the informed consent.
3. The subject is scheduled to undergo an indicated primary abdominal or thoracic procedure for resection, transection and creation of anastomosis per the IFU where the Signia™ Stapling System using Endo GIA™ with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads will

be used per its IFU. (See Section 18.1 Appendix A for Reloads to be assessed in this study) Additionally, if considered appropriate for the procedure only Medtronic buttresses can be used during the course of the study.

a. Thoracic procedures may include, but are not limited to wedge resection and lobectomy, and may include video assisted thoracic surgery (VATS) or open procedures
b. Abdominal procedures may include, but are not limited to, laparoscopic sleeve gastrectomy (LSG), laparoscopic Roux-en-Y gastric bypass (LRYGB)

8.4. Exclusion Criteria

1. Subjects undergoing cardiac and vascular procedures
2. The procedure is an emergency procedure
3. The procedure is a revision/reoperation of a primary operation
4. Any female subject who is pregnant
    a. Females of child-bearing potential will be required to provide either a urine pregnancy test or serum pregnancy test during Screening and confirmed on the day of operation (except for subjects who are surgically sterile or are post-menopausal for at least two years) (USA only) and per EU local requirements
5. Any subject who is considered to be part of a vulnerable population (e.g. prisoners or those without sufficient mental capacity)
6. The subject is unable or unwilling to comply with the study requirements or follow-up schedule
7. The subject has comorbidities which, in the clinical judgment of the Investigator, will not be appropriate for the study or the subject has an estimated life expectancy of less than 6 months
8. The subject has been diagnosed with a bleeding disorder and/or is undergoing active and not reversed anticoagulant treatment.
9. The subject is concurrently enrolled in another investigational drug or device research study or has been enrolled in another study within 30 days of enrollment.

Pre-existing/chronic conditions specific to Endo GIA™ Reloads with Tri-Staple™ Technology and Tri-Staple™ 2.0 Cartridge contraindications as described in the IFU, respectively.

9. Study Procedures

9.1. Schedule of Events

9.1.1. Study schematic

Procedure/Assessment	Screening (Day -30 to 0)	Operative (Day 0)	Discharge Assessment	Follow-up Assessment (at 30 Days (+14 days))
	Can be combined			
Informed Consent[1]	X			
Eligibility Criteria	X	X		
Pregnancy check via urine or serum pregnancy test females of child bearing potential (USA only) or per EU local requirements	X[2]	X[2]		
Demographic Data	X			
Vital Signs	X	X		
BMI	X			
Abbreviated Physical exam[3]	X	X		
Medical and surgical history, including previous abdominal or thoracic surgical history	X			
American Society of Anesthesiologists (ASA) grade		X		
Operative date		X		
Operative start/stop times		X		
Type of procedure		X		
Anesthesia details		X		
Study device data[4]		X		
Use of feedback display (if applicable)		X		
Concomitant medications[5]		X	X	X
Procedure Related Adverse Events		X	X	X
Adverse Device Effects (ADEs)		X	X	X
Staple line assessment		X		
Device deficiencies/ malfunctions[6]		X		
Device Accountability		X		
Length of hospital stay			X	
Length of intensive care stay (if applicable)			X	
Surgical site and infection assessment by the Investigator according to the standard of care and site policy, ex. Positive wound culture			X	X
Readmission- related to primary procedure				X

1. No study procedures will be performed until informed consent form has been completed. Subject should be re-consented if date of original consent is greater than 30 days.

Procedure/Assessment	Screening (Day -30 to 0)	Operative (Day 0)	Discharge Assessment	Follow-up Assessment (at 30 Days (+14 days))
	Can be combined			
2. If Screening and Surgery occur on different days, these procedures should occur during Screening and be reconfirmed on the day of surgery. 3. Including height, weight, and examination of the heart, lung, and abdomen as applicable 4. Including but not limited to, staple size, number of firings, type of reload used, location of firings, lot number of devices used, malfunctions 5. Only those related to relevant medical history or adverse events will be collected, e.g.: anticoagulants, blood pressure, antibiotics, pain medications 6. Including but not limited to system set-up (insertion guide, power shell), OLED screen display, rotation, articulation, clamp/unclamp, firing, use of manual retraction tool				

9.2. Subject Screening

A screening visit will be performed within 30 days up to the day of the scheduled procedure and may be combined with the surgery procedure visit. Subjects will be consented prior any procedures specific to the study are undertaken. The purpose and all aspects of the study will be explained to the subject. Subjects who agree to study participation must sign and personally date the sponsor and an IRB/EC-approved informed consent form prior to participating in any study activities.

Once informed consent has been completed according to IRB/IEC requirements and eligibility is confirmed, the subject's demographics and medical history will be assessed to include:

- Eligibility Criteria
- Subject demographics (e.g., sex, age, ethnicity and race if allowed per local regulations)
- Medical and surgical history (previous abdominal or thoracic surgical history, smoking history, anticoagulant therapies and prevalence of diabetes)
- Vital signs (heart rate, temperature, respiratory rate, blood pressure)
- Oxygen saturation levels (pulse oximeter)
- BMI
- Abbreviated physical exam, including height, weight, and examination of the heart, lung, and abdomen
- Serum or urine pregnancy test females of child bearing potential (USA only) or per EU local requirements

9.3. Prior and Concomitant Medications

Any prior or concomitant medication is allowed for this study at the discretion of the on-site physician. Prior or concomitant medications related to relevant medical history or adverse events will be collected (e.g.: anticoagulants, blood pressure, antibiotics, pain medications).

9.4. Subject Consent

Subjects (or legally authorized representatives) will be consented in the study prior to any procedures specific to the study are undertaken. Subjects (or legally authorized representatives) will be provided with a description of the device and procedure; risks, benefits, and alternative procedures; length of participation required; and information regarding injury and confidentiality. Subjects (or legally authorized representatives) will be informed that their participation in this study is voluntary and they may refuse to participate or discontinue from the study at any time. Subjects (or legally authorized representatives) will be given the opportunity to ask the Investigator questions so that they are adequately informed about the research. The informed consent form must be personally signed and dated by subject (or legally authorized representative) and Investigator or an authorized designee responsible for conducting the informed consent process at time of consent. The informed consent process will be documented in the source records and a copy of the consent will be provided to the subject (a signed copy where applicable). If the subject (or legally authorized representative) completed consent form outside of 30 days screening window, a new consent must be signed/dated prior to surgery.

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The investigator or his/her authorized designee should inform the subject in a timely manner.

Medtronic will revise the written Patient Information and Informed Consent Form whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The revised information will be sent to the investigator for approval by the EC/IRB. After approval by the EC/IRB, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

9.5. Randomization and Treatment Assignment

No randomization will occur during the course of the study.

9.6. Medication Compliance

Medication is not restricted during the course of this study and will be at the discretion of the on-site physician. Concomitant medications relevant to adverse events will be collected (e.g.: anticoagulants, blood pressure, antibiotics, pain medications).

9.7. Assessment of Efficacy

Primary assessment will examine the incidence of subjects reporting serious adverse device effects up to and including 30 (+14) days postoperative and device deficiencies/malfunctions affecting the intended

performance will be recorded in the eCRF and used to assess the efficacy of the Signia™ stapling system. In addition, the following assessments will be collected:

9.7.1. Operative (Day 0)

The Study Investigator should perform the surgical procedure according to the appropriate standard procedures and practices at his/her institution using the Signia™ Stapling System. Additionally, the following procedures and assessments will be performed:

- Eligibility Criteria*
- Vital signs (heart rate, temperature, respiratory rate, blood pressure, pulse, oxygen saturation levels)*
- Abbreviated physical exam, including height, weight, and examination of the heart, lung, and abdomen*
- American Society of Anesthesiologists (ASA) grade (See Appendix B, Section 18.2)
- Serum or urine pregnancy test females of child bearing potential (USA only) or per EU local requirements *

* Assessments only need to be repeated if Screening/Operative Visit occur on different days

- Operative date
- Operative start (skin incision) and stop times (skin closure)
- Type of procedure
- General anesthesia information (type, start and stop times)
- Study device data (i.e., type of reload used, staple size, lot number of devices used, number of firings, location of firings)
- Use of Signia feedback display (if applicable)
- Relevant concomitant medications (only those related to relevant medical history or adverse events will be collected e.g.: anticoagulants, blood pressure, antibiotics, pain medications)
- Procedure related adverse events
- Adverse device effects (ADEs) (ADEs, as defined by ISO14155-2011, see section 11.1.3 for additional details)
- Staple line assessment
- Device deficiencies/malfunctions affecting intended performance to include but not limited to;
    - System set-up (insertion guide, power shell)
    - Organic light emitting diode (OLED) screen display
    - Rotation
    - Articulation
    - Clamp/UnClamp
    - Firing
    - Use of manual retraction tool

- User errors
- Unintended cutting
- Insufficient staple deployment
- Inability to complete the firing sequence
- Stapling without cutting

- Device accountability

9.7.2. Discharge Assessment

On the day of discharge the following assessments will be made:

- Procedure related adverse events
- Adverse device effects (e.g. air leak, anastomotic leak, staple line bleeding, peritonitis, sepsis, intracavitary infection, intervention or reoperation)
- Length of hospital stay
- Length of intensive care unit stay (if applicable)
- Surgical site and infection assessment by the Investigator according to the standard of care and site policy, ex. Positive wound culture
- Relevant concomitant medications (only those related to relevant medical history or adverse events will be collected e.g.: anticoagulants, blood pressure, antibiotics, pain medications)

9.7.3. Follow-up Assessments (Day 30 +14 days))

On post-operative day 30, assessments will take place by delegated study personnel. Assessments will include:

- Readmission related to primary procedure
- Procedure related adverse events
- Adverse device effects (ADEs)
- Surgical site and infection assessment by the Investigator according to their the standard of care and site policy, ex. Positive wound culture
- Relevant concomitant medications (only those related to relevant medical history or adverse events will be collected e.g.: anticoagulants, blood pressure, antibiotics, pain medications)

After the study has been completed no further study specific medical care will be provided and subjects will receive standard of care.

9.8. Assessment of Safety

Safety will be assessed by monitoring the occurrence of adverse events (AEs), serious adverse events (SAEs), death, adverse device effects (ADE), unanticipated serious adverse device effects (USADE), device deficiency/malfunction, and/or device misuse. Assessments will take place during the procedure through post-operative day 30 (+14 days) and will be recorded in the eCRF.

9.9. Recording Data

This study will utilize an electronic database and eCRF. All data requested on the eCRF are required. Study visits or measurements not collected and/or recorded will be considered deviations unless otherwise specified. The Principal Investigator or authorized designee(s) must ensure the accuracy and completeness of the recorded data and then provide his/her electronic signature on the eCRFs. The Investigator's electronic signature for specific eCRFs will be documented in compliance with local regulations and compliance with the protocol. Changes to data previously submitted to the sponsor will require a new electronic signature by the Investigator to acknowledge/approve the changes.

9.10. Deviation Handling

The Investigator is not allowed to deviate from the CIP, except under emergency circumstances to protect the rights, safety and well-being of human subjects, otherwise no changes to the protocol will be permitted without the written approval from Medtronic, the IRB/EC and Competent Authority. The investigator must notify Medtronic and the reviewing IRB/EC of any deviation from the Investigational Plan. The deviation will be recorded in the eCRF and such notice must be given as soon as possible, but in no event later than 5 working days after the emergency has occurred. Except in such an emergency, prior written approval by Medtronic is required for changes in or deviations from the Plan. If these changes or deviations affect the scientific soundness of the Plan or the rights, safety, or welfare of human subjects the IRB/EC will also be notified. All other deviations will be reported per the site's IRB/EC deviation policy. Should any deviations from the Investigational Plan occur, these will be reviewed by Medtronic for their clinical significance and compliance to the protocol. Repetitive or serious investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases, freeze enrolment or ultimately terminate the Investigator's participation in the clinical study.

If it is discovered that an investigator is not complying with the signed Investigator Agreement, the investigational plan, applicable laws, or any conditions of approval imposed by the reviewing IRB/EC, the monitor will report to the Sponsor and take such steps necessary to promptly secure compliance. If compliance cannot be secured, device shipments to the investigator may be discontinued and the investigator's participation in the investigation terminated. The monitor shall also require such an

investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

9.11. Subject Withdrawal or Discontinuation

9.11.1. Enrolled

A subject is considered enrolled in the study when it is confirmed they meet inclusion and exclusion criteria and ICF is signed and dated by subject and the Investigator and must be followed for the full 30 days if the procedure was begun or completed with the study device. Enrollment can take place 30 days before procedure and subjects will be followed for 30 (+14) days postoperative. If enrollment occurs greater than 30 days prior to procedure the subject will require to be reconsented.

9.11.2. Screen Failure

Subjects who provide study consent, but then are determined to be ineligible prior to the procedure with the study device will be considered a screen failure and will not require additional study follow-up visits. The reason for the screening failure will be clearly delineated on the applicable eCRFs.

9.11.3. Discontinuation

Subjects who provide study consent, and are deemed eligible, but for which do not undergo the procedure with the study device will be considered “discontinued” and will be followed until discharge. These subjects will only contribute AE data intra-operatively until discharge (no additional follow-up). Follow up of subjects withdrawn or discontinued will be determined by investigator. Safety and device deficiency data will not be collected from the discontinued population.

9.11.4. Withdrawal

The reason for study exit, including screen failure, will be documented on the applicable electronic case report form (eCRF). In the event the subject withdraws consent during the study, the date of withdrawal will be documented. If the Study Investigator voluntarily removes a subject from further study participation, supporting documentation must be in place for the rationale and date of removal. Follow up of subjects withdrawn or discontinued will be determined by investigator.

9.11.5. Lost to Follow-up

Every attempt will be made to contact subjects that are noncompliant with study procedures. Subjects will be considered lost to follow-up once the following steps have been taken:

- Two phone calls should be made to the subject. Each attempt should be clearly documented in the source documents and the response or lack thereof should be captured.
- If there is no response to the phone calls, then an official, certified letter should be written to the subject. A copy of the letter and return or delivery receipts should be retained in the subject's source document.
- When all due diligence attempts to contact have been made, after a period of two (2) weeks, the subject will be considered Lost to Follow-up. The Sponsor must be notified and the End of Study (EOS) form must be completed.

10. Risks and Benefits

10.1. Potential Risks

Surgeons participating in this study are experienced with the known risks related to standard of care for abdominal and thoracic surgeries. Risks associated with participation in the clinical investigation and use of the Signia™ Stapling System with approved reloads in abdominal and thoracic procedures include, but are not necessarily limited to: adhesions, air leak, anastomotic leakage, atelectasis, bile leak, biliary fistula, bleeding, bronchopneumonia, cardiac complications, death, gastric leak, heart failure, hematoma, infection, inflammation, intra-abdominal fluid collection, liver failure, pleural effusion, pneumothorax, pulmonary embolism, stricture, ulceration, and wound dehiscence.

The instructions for use (IFU) will guide surgeons on proper use of the device. Surgeons and site staff will undergo training on the device prior to participation in the study.

Animal studies to evaluate the potential for AEs on reproductive ability and effects on the embryo/fetus have not been conducted. As with any device, there is always a risk of a rare or previously unknown side effect developing from the treatment or use of the device.

The risk analysis reports are based on the operation of Signia™ Stapling System by trained personnel. According to the Risk Analysis Chart, there were no unacceptable residual risks in the Zone 3 category (red) proceeding mitigation activities. The following are all residual risks that exist in a Zone 2 category (yellow) proceeding mitigation activities for the Signia™ Stapling System. These risks do not directly result from design or manufacturing failures, so the risk has been reduced as far as possible with appropriate mitigation controls in place:

- Non-sterile product
- EtO Residuals
- Exposure to Bio-Hazard
- Difficult Insertion through Port or Organ
- Non-functional Staple Closure (identified Intra- or Post- Operatively)

- Unintentional Firing
- Device Cuts without Stapling
- Reload Locks on Tissue
- Uncontrolled Rotation or Articulation
- Loss of Tissue Sensing Speed Control
- Reload De-articulates when Clamped on Tissue

The overall residual risk after design risk mitigation strategies and/or design control was deemed acceptable in the Risk Management Reports for the Signia™ Stapling System.

10.2. Potential Benefits

The information obtained from this study will be used to confirm the safety and performance of the Signia™ Stapling System. This information may or may not lead to findings that could result in a reduction of complications for future patients.

10.3. Risk-Benefit Rationale

A positive risk/benefit ratio has been demonstrated with the Signia™ Stapling System with appropriate reloads as evidenced by preclinical and biocompatibility testing.

The Signia™ Stapling System is a class II FDA 510K cleared product, and a MDD class IIa and class I CE-marked product. Consequently, the Signia™ Stapling System presents a favorable risk/benefit ratio to the subject. The instructions for use (IFU) in addition to surgeon training, will instruct surgeons on proper use of the device to mitigate risk. There are currently no known interactions between the Signia™ Stapling System and concurrent medical interventions.

11. Adverse Events and Device Deficiencies

Adverse event (AE) definitions used in this study are based on ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects -- Good Clinical Practice).

Foreseeable adverse events and anticipated adverse device effects can be found in the instructions for use. The instructions for use (IFU) in addition to surgeon training, will instruct surgeons on proper use of the device to mitigate these risks.

11.1. Definitions/Classifications

11.1.1. Adverse Event (AE)

In alignment with ISO 14155:2011 (Section 3.2), an Adverse Event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

This definition includes events related to the study device and the procedures involved. For users or other persons, this definition is restricted to events related to study devices.

For study purposes, the following occurrences are considered to be expected observations following surgical procedures (primarily associated with anesthesia) and will not be considered reportable AEs, as long as the event is not associated with significant sequelae, does not prolong hospitalization, and responds to standard medical therapy:

- Postoperative transient nausea determined to be procedure related within the first 24 postoperative hours.
- Postoperative transient emesis determined to be procedure related within the first 24 postoperative hours.
- Postoperative constipation, determined to be procedure and/or medication related for the duration of medication administration for management of pain.
- Postop pain that the Investigator considers common and within normal limits for the procedure and is well-managed with medication.

For study purposes procedure related adverse events will be collected and documented at the time of the procedure and up to and including the 30 day (+14 days) post-operative follow up visit.

11.1.2. Serious Adverse Events (SAE)

In alignment with ISO 14155:2011 (Section 3.37), a serious adverse event (SAE) is any AE that has:

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

NOTE: Planned hospitalization for a pre-existing condition or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered an SAE.

SAEs will be collected and documented at procedure and up to and including the 30 day (+14 day) post-operative follow-up visit.

11.1.3. Adverse Device Effect (ADE)

In alignment with ISO 14155:2011 (Section 3.1), an Adverse Device Effect is an adverse event related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any deficiency/malfunction of the investigational medical device.

This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Adverse Device Effects will be reported by the Investigator(s). If escalation is required (due to the potential need for reporting) ADEs will be reviewed by Medtronic Medical Affairs. Both confirmed and possible adverse device effect events will be included in the study report.

Examples of adverse device effects include but are not limited to: leaking or bleeding due to non-functional staple closure, damage to surrounding tissue due to unintentional firing, unintentional tissue loss due to reload locks on tissue

ADEs will be collected and documented at procedure and up to and including the 30-day follow-up visit.

11.1.4. Serious Adverse Device Effect (SADE)

In alignment with ISO 14155:2011 (Section 3.36), a Serious Adverse Device Effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

SADEs will be collected and documented at procedure and up to and including the 30-day follow-up visit.

11.1.5. Unanticipated Serious Adverse Device Effect (USADE)

In alignment with ISO 14155:2011 (Section 3.42), an Unanticipated Serious Adverse Device Effect is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

USADEs will be collected and documented at procedure and up to and including the 30-day follow-up visit.

11.1.6. Device Deficiencies

In alignment with ISO14155:2011 (Section 3.15), a Device deficiency is an inadequacy of a medical device-related to its identity, quality, durability, reliability, safety or performance; such as malfunction, misuse or use error and inadequate labeling.

All Signia™ Stapling System device deficiencies/malfunctions will be documented on the Device Deficiency/Malfunction eCRF.

In the event of a device deficiency the device should be returned to Covidien for analysis, if possible. Instructions for returning the study device will be provided. Device deficiencies should also be documented in the subject's medical record.

Device deficiencies are NOT to be reported as AEs.

However, if there is an AE that results from a device deficiency, that specific event would be recorded on the appropriate eCRF.

11.1.7. Adverse Event Severity Classification

Severity will be defined according to the following criteria:

Mild	Awareness of event, but easily tolerated
Moderate	Discomfort enough to cause some interference with activities of daily living (ADL)
Severe	Incapacitating, with an inability to perform ADL
Death	Death related to AE

An AE can be classified as severe and not deemed an SAE. Similarly, an SAE is not automatically severe in nature.

11.1.8. Adverse Event Relationship Classification

Causality assessments define the relationship between the use of the medical device (including the medical-surgical procedure) and the occurrence of each adverse event, according to MEDDEV (Guidelines on Medical Devices, Clinical Investigations: Serious Adverse Event Reporting). The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

Each AE will be classified according to five different levels of causality. The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational medical device or procedures:

Not related: relationship to the device or procedures can be excluded when:

1. the event is not a known side effect of the product category the device belongs to or of similar devices and procedures
2. the event has no temporal relationship with the use of the device or the procedures;
3. the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
4. the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
5. the event involves a body-site or an organ not expected to be affected by the device or procedure;
6. the serious 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);
7. the event does not depend on a false result given by the device used for diagnosis, when applicable;
8. harms to the subject are not clearly due to use error;
9. In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious 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/ clinical condition or/and an effect of another device, drug or treatment). Cases were 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 serious event is associated with the device or with procedures beyond reasonable doubt when:

1. the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
2. the event has a temporal relationship with device use/application or procedures;
3. the event involves a body-site or organ that
    a. the device or procedures are applied to;
    b. the device or procedures have an effect on;
4. the serious event follows a known response pattern to the medical device (if the response pattern is previously known);

5. 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 serious event (when clinically feasible);
6. other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
7. harm to the subject is due to error in use;
8. the event depends on a false result given by the device used for diagnosis, when applicable;
9. In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The Sponsor and the Investigators will distinguish between the serious adverse events related to the device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the device. Complications of procedures are considered not related if the said procedures would have been applied to the subjects also in the absence of device use/application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where the sponsor remains uncertain about classifying the serious event, it should not exclude the relatedness and classify the event as “possible”.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse (device) events. The occurrence of unanticipated events related to the use of the device (USADE) could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand

11.1.9. Adverse Event Outcome Classification

Outcome of the event will be defined according to the following:

- ***Fatal****:* This event is determined to be the cause of death.
- ***Not Recovering/Not Resolved***: The event has retained pathological conditions resulting from the prior disease or injury.
- ***Recovered/Resolved****:* The event has fully resolved at the end of the study.
- ***Recovering/Resolving****:* The event is ongoing at the end of the study.
- ***Unknown***: The event has been unclassified at the end of the study.

11.2. Reporting of Adverse Events

The following events are generally considered reportable during the course of this study and should be reported to the sponsor:

- any device related AE, SADE, SAE, or USADE

- any Device Deficiency/Malfunction that might have led to a SADE if
    - suitable action had not been taken or
    - intervention had not been made or
    - if circumstances had been less fortunate
- new findings/updates in relation to already reported events.

Events will be reviewed by the sponsor to determine any reporting obligations to National Competent Authorities and IRBs/ECs.

The following table captures the reporting requirements for this study. Local and regional regulatory requirements shall be followed in addition to study requirements.

Type of Event	Timeframe	Submit to
Any Death	**As soon as practicable** but no more than 10 work days after the day that you become aware of information from any source, that reasonably suggests that a device has or may have caused or contributed to the death of a patient of your facility	Sponsor/ Device Manufacturer and Local (IRB/ EC) and regional regulators (FDA)
UADE	**As soon as possible,** but in no event later than 10 working days after the investigator first learns of the effect.	Sponsor / Device Manufacturer and any local/ regionally required regulators
All Serious Events including SAEs, USADEs, Serious Injuries or Significant Safety Issues	**Within 24 hours, but no later than 10 work days (and/or per local requirements)** after the day that investigator becomes aware of information, from any source, that reasonably suggests that a device has or may have caused or contributed to a serious injury to a patient of your facility.	Sponsor / Device Manufacturer and as per local reporting requirements.

Assessment of the occurrence of an AE will be based on changes in the subject's abbreviated physical examination, laboratory results and/or signs and symptoms. Adverse events will be monitored until a subject completes the study unless the Investigator determines the event is related to the device, in which case they will be monitored until resolution if possible. Medical care will be provided, as defined in the informed consent, for any AE related to study participation. Adverse events will be collected on an AE eCRF and applicable source documentation. To the extent possible, the event to be recorded and reported is the event diagnosis as opposed to event symptoms (e.g., fever, chills, nausea and vomiting in the presence of a clinically diagnosed infection is to be reported as infection only). For the purposes of this protocol, only those AEs occurring after enrollment will be recorded.

The following should not be considered an AE:

- A condition requiring a preplanned procedure unless the condition worsened since screening
- A preexisting condition found as a result of screening, unless the condition has worsened since enrollment.

All responses to the above events that require treatment beyond the institution's standard procedures will be reported as AEs.

All device and procedure related AEs observed during the course of this study (up to and including the 30day follow up visit), regardless of severity or relationship to the device will be recorded on the appropriate eCRF.

11.3. Study Contact Information

Questions regarding safety or medical procedures should be directed to Medtronic MITG Medical Affairs. All other questions including emergency contact for reporting serious adverse events and serious adverse device effects should be directed to Medtronic MITG Surgical Innovations, Clinical Research.

Medical Affairs	
Christine Mauro, MD, MMSc Director, Medical Affairs Medtronic MITG Surgical Innovations 555 Long Wharf Drive New Haven, CT 06511 USA Phone: 203-361-8276 Christine.Mauro@medtronic.com	Matthew Savary, MD Director, Medical Affairs Medtronic MITG 5920 Longbow Drive Boulder, CO 80301 USA Phone: 203.530.1395 Matthew.Savary@medtronic.com

12. Data Review Committees

12.1. Safety Committee

An internal Medtronic Safety Team will review the overall rates of protocol defined adverse events (SAEs and events related to the primary and secondary endpoints) on a quarterly basis. The committee will have the ability to make recommendations and request further information as required.

12.2. Independent Medical Monitor

Medtronic will utilize an Independent Medical Monitor to provide an independent adjudication of pre-specified adverse events in support of protocol defined endpoint data. The Independent Medical Monitor will be a qualified, board-certified surgeon that is not affiliated with an investigative center. The Independent Medical Monitor will contribute to safety aspects of the clinical study and will conduct the study Safety Review Meetings and will review the key events and data in the event of Serious Adverse Events.

The Independent Medical Monitor will be blinded to the investigational sites.

12.3. Steering Committee

The Steering Committee will consist of Investigators participating in this study, as well as appropriate members of Medtronic Clinical and Medical Affairs. The role of the Steering Committee is to make recommendations on the design and conduct of the study, the analysis of data, and the communication of results in alignment with the Medtronic Publication and Authorship Policy. The Steering Committee will also review aggregate adverse event data on an as needed basis, as described in the Steering Committee Charter.

13. Statistical Design and Methods

13.1. Statistical Test Methods

Continuous variables will be summarized using counts, means, standard deviations, medians, minimum and maximum. Categorical variables will be summarized using frequencies and percentages. Changes to the planned statistical analysis as defined in the protocol will be documented in the statistical analysis plan and clinical study report.

13.2. Sample Size Determination

Sample size was determined based on the primary endpoint (incidence of subjects reporting serious adverse device effects (ADEs) up to and including 30 days including intra- and post-operative leaks), but considering an acceptable probability (≥ 80%) to observe at least one adverse device effect (ADE) within 30 days, in each arm (abdominal or thoracic indication).

A previous Medtronic study (ClinicalTrials.gov ID NCT02500537) conducted on N=100 subjects and evaluating an equivalent device (Endo GIA™ Reinforced Reload with Tri-Staple™ Technology) in the same indications and with a similar design and follow-up reported the following adverse device effects rates (described as "device related adverse events" with the study protocol and final report):

	Abdominal	Thoracic
Adverse device effect incidence	3.3%	2.5%

Because of the expected low adverse device effect incidence rate (<5%) in the Abdominal or Thoracic procedures, as described above, a Poisson distribution is applied to estimate the probability of observing AE event(s).

In the Abdominal indication, for an anticipated sample size of 53 subjects using an adverse device effect rate of 3.3%, and including a 5% attrition rate within 30 days, we obtain a probability of 81% to observe at least 1 adverse device effect.

In the Thoracic indication, for an anticipated sample size of 74 subjects using an adverse device effect rate of 2.5%, and including a 5% attrition rate within 30 days, we obtain a probability of 83% to observe at least 1 adverse device effect.

For the overall population (in both indications), with a sample size of 127 subjects and considering an averaged adverse device effect rate of 2.9%, and including a 5% attrition rate within 30 days, we obtain a probability of 97% to observe at least 1 adverse device effect, and a probability of 86% to observe at least 2 adverse device effects.

In any scenario, we will have ≥ 80% probability to observe at least 1 adverse device effect in each arm.

13.3. Analysis Population

The full analysis set (FAS) will consist of all enrolled and treated subjects (using Signia™). For this study the full analysis set corresponds to the safety population. FAS will serve as the primary analysis population for safety and performance analyses, as well as for demographics and baseline data analysis.

The per protocol (PP) population will consist of all subjects from the FAS population who do not have a major protocol violation. Analyses on the PP population will provide supporting evidence to the primary results (obtained on FAS).

13.4. Statistical Analysis Endpoints

13.4.1. Primary Endpoint

The primary endpoint is the incidence of subjects reporting serious adverse device effects up to and including 30 days (+14days) post-procedure which utilizes the Signia™ Stapling System. It will be summarized using descriptive statistics.
A two-sided 95% confidence interval will also be calculated. The acceptance criteria for this endpoint is an upper limit of the 95% CI below 20%.
The analysis will be performed in abdominal group and in thoracic group, and in the combined groups.

13.4.2. Secondary Endpoint

The incidence of secondary outcome measures will be summarized using descriptive statistics:

- counts and percentages for categorical data
- mean, standard deviation, median, minimum and maximum for quantitative data.

13.5. Handling of Missing Data

No data imputation will be performed for missing data unless otherwise noted in statistical analysis plan. All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection.

Sample size has been determined including an attrition rate of 5% within 30 days for primary endpoint analysis.

13.6. Interim Analysis

A preliminary analysis will be conducted in the study when 64 enrolled subjects complete the 30 day follow up visit. The objective is to confirm early safety of the product. This interim analysis data review is driven by regional needs, to support a regulatory submission.

14. Ethics

14.1. Statement(s) of Compliance

This clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, Good Clinical Practice guidelines, ISO14155:2011, and any regional or national regulations such as FDA regulations (USA), as appropriate. All principles of the Declaration of Helsinki have been implemented in this clinical study by means of the subject informed consent process, IRB/EC approval, clinical study training, clinical study registration, publication policy.

The clinical investigation will not begin until all necessary approvals/favorable opinions are obtained from the appropriate IRB/EC or regulatory authority, as appropriate. Should an IRB/EC or regulatory authority impose any additional requirements, they will be followed.

Information regarding the study and study data will be made available via publication on clintrials.gov. Additionally, the results of this study will be offered for publication at the conclusion of the study, if participating investigators believe the data warrants publication in an appropriate journal.

15. Study Administration

15.1. Monitoring

Site visits will be conducted by an authorized Medtronic representative to qualify potential sites, conduct site initiation, ensure compliance, assess informed consent process, conduct interim monitoring visits to monitor study data, subjects' medical records, eCRFs, device accountability, device use and storage, IRB/EC submissions, regulatory binder in accordance with current protocol, GCPs and the respective local and national regulations and guidelines (as applicable) as well as close-out site activities. The Study Investigator and the investigating site will permit authorized clinical research personnel from Medtronic or contracted by Medtronic to review completed eCRFs, IRB/EC decisions, and Investigator and clinical site records at regular intervals throughout the study as well as permit study-related monitoring, audits, EC/IRB review, and regulatory inspection(s) by providing direct access to source data/documents. Additionally, subject charts and clinical records will be requested and reviewed so that protocol adherence and source documentation can be verified. In instances where data protection regulations prohibit the direct examination of hospital records by the study Sponsor or designee(s), the Investigator will cooperate in a method of source data verification with the Sponsor detailed in the monitoring plan. Monitoring may be performed with in person visits or remotely, when applicable.

To ensure the rights, safety, and welfare of study subjects are being maintained, the monitor will maintain assurance that all study staff are trained on the study protocol and use of the study devices. If

the monitor discovers that an investigator is not complying with the signed Investigator Agreement, the investigational plan, applicable laws, or any conditions of approval imposed by the reviewing IRB/EC, the monitor will report to the Sponsor and take such steps necessary to promptly secure compliance. If compliance cannot be secured, device shipments to the investigator may be discontinued and the investigator's participation in the investigation terminated. The monitor shall also require such an investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

15.2. Data Management

Data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the remote data capture (RDC) system and will be issued to the site for appropriate response. The site staff will be responsible for resolving all queries in the database within 60 days. Medications will be coded under the WHO dictionary while Medical History, Surgical History and/or Adverse Events will be coded in Medical Dictionary for Regulatory Activities (MedDRA). Any data to be recorded directly on the CRFs and to be considered source data

This study will be using a USA FDA 21 CFR Part 11 compliant electronic data capture system. All system level validation documentation is retained within the Information Systems group.

15.3. Direct Access to Source Data/Documents

Investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), and provide direct access to source data/documents as per local policies and regulations.

15.4. Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations.

Subject names will be kept confidential. Only the site id number and subject number will be recorded in the eCRF, and if the subject name appears on any other document, it must be redacted. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the sponsor, IRBs/ECs, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. Subjects will also be informed that information regarding the study that does not include subject identifiers will be posted on the USA FDA required study registry, clinicaltrials.gov and/or other regional registries/local public database if required.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a subject master list to enable subjects' records to be identified.

15.5. Liability

Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the IRB/EC.

15.6. CIP Amendments

A CIP/Protocol amendment will be prepared when there are revisions that are significant changes or corrections, or modifications that impact subject safety, ethical conduct, data integrity or study design. CIP/Protocol amendments must undergo review and approval by the sponsor, IRB/EC and any appropriate regulatory authority, and will be logged in the document version history (Section 18). IRB/EC approval, regulatory authority approval, site training and a new Acknowledgement form will be signed and returned before any new procedures take place.

15.7. Record Retention

The investigator and the sponsor will maintain the records of the study including all pertinent correspondence, the study protocol with any/all amendments, all correspondence with and approval from the IRB/EC, the clinical trial agreement, the Investigator Agreement, device accountability records, individual subject records, signed informed consent forms copies of signed and dated CRFs (or equivalent), records of AEs and ADEs reported to sponsor and final report (including any statistical analyses). Subject files, other source data and essential documentation kept in the Investigator study files, must be kept for a period of no less than 2 years after the latter of the following two dates: the date on which this investigation is terminated or completed. Records may need to be maintained by the Principal Investigator for a longer duration if national regulations require or if agreed to in writing with Medtronic. All data and documents should be made available if requested by relevant authorities.

15.8. Publication and Use of Information

The Medtronic Publication and Authorship Policy is aligned with the International Committee of Medical Journal Editors (ICMJE) recommendations (www.icmje.org). Medtronic will seek to publish, in appropriate peer-reviewed journals and scientific conferences, results of clinical studies where human subjects are involved, regardless of outcome. While study results are owned by Medtronic, all data on which a publication is based will be made available to all authors as required for their participation in

the publication process. Furthermore, data may be published or used by study investigators provided that such publication or use is in accordance with this this protocol, the Medtronic Publication and Authorship Policy, and the Clinical Investigation Agreement. Investigators must submit a copy of all manuscripts and/or abstracts to Medtronic for review and comment 30 days prior to planned submission. Medtronic acknowledges that its right to review and comment shall relate solely to the proprietary, licensing, and/or confidential rights Medtronic may have in such proposed publication, rather than whether such results and/or opinions are favorable to Medtronic.

The publication of post-hoc analyses, regional results, or single-center experiences based on multicenter clinical studies should not precede that of the primary multicenter publication, and should cite the primary publication whenever possible, as required by specific journal and scientific meeting guidelines.

Medtronic involvement in a publication (e.g., funding of the study; sponsor of the study; collection, analysis, and interpretation of data; professional writing assistance) must be disclosed according to journal-specific policies, submission requirements, and prevailing editorial standards, in addition to those specified by International Committee of Medical Journal Editors. Authors must ensure that an acknowledgement/disclosure statement is included in the body of the manuscript for Medtronic to review for accuracy. All authors must also disclose financial or personal affiliations that could be considered conflicts of interest as per journal/conference requirements.

To enable health care providers, payers, and subjects access to the wealth of Medtronic's research, Medtronic will report its scientific data in accordance with the principles outlined in the Guidance Document on Registration and Reporting Results of Company-Sponsored Clinical Trials under FDAAA 2007 (Title VIII).

15.9. Suspension or Early Termination

Medtronic or appropriate regulatory authorities reserve the right to suspend or discontinue the study at any stage, with written notice to all investigators, all institutions, all reviewing IRBs (USA), any investigator(s) in communication with the EC (EU) , all subjects and subjects' personal physicians and any applicable regulatory agencies. Similarly, investigators may withdraw from the study at any time, subject to providing written notification to Medtronic 30 days prior to the date they intend to withdraw. However, Medtronic and investigators will be bound by their obligation to complete the follow-up of subjects already enrolled in the study. The subjects must be followed according to the clinical protocol, and information obtained during subject follow-up shall be reported to Medtronic on the appropriate eCRF.

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17. Version History

Version	Summary of Changes	Author(s)/Title

1.0	• 'Not Applicable, New Document'	Nicholas Paquette, Senior Medical Writer
2.0	• Removed Multi-use (MULU) Signa reloads from plan, replaced with single use reloads (Endo GIA™ Reloads with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads) • Removed clinician questionnaire • Added interim analysis • Update EU regions	Greg Sindberg Senior Medical Writer
3.0	• Changed site language to "approximately 10 sites in the USA and Europe (potentially in United Kingdom, Spain, Italy)" based on compliance recommendations	Greg Sindberg Senior Medical Writer

18. Appendices

18.1. APPENDIX A: Endo GIA™ with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads

Endo GIA™ with Tri-Staple™ Technology and Tri-Staple™ 2.0 Intelligent Reloads that are appropriate for use in this study:

Standard Reload	EGIA45AV*	Gray
	EGIA45AVM	Tan
	EGIA45AMT	Purple
	EGIA60AVM	Tan
	EGIA60AMT	Purple
Tri-Staple™ 2.0 30 mm Reload	SIG30AV*	Gray
	SIG30AVM	Tan
	SIG30AMT	Purple
Tri-Staple™ 2.0 Curved Tip Reload	SIG30CTAV*	Gray
	SIG30CTAVM	Tan
	SIG45CTAV*	Gray
	SIG45CTAVM	Tan
	SIG45CTAMT	Purple
	SIG60CTAVM	Tan
	SIG60CTAMT	Purple
Tri-Staple™ 2.0 Radial Reload	SIGRADVM	Tan
	SIGRADMT	Purple
	SIGRADXT	Black
Tri-Staple™ 2.0 Black Reload	SIG45AXT	Black
	SIG60AXT	Black
Endo GIA™ Reinforced Reload with Tri-Staple™ Technology	EGIATRS45AMT	Purple
	EGIATRS45AXT	Black
	EGIATRS60AMT	Purple
	EGIATRS60AXT	Black

18.2. APPENDIX B: American Society of Anesthesiologists (ASA) Physical Status Grading System

Last approved by the ASA House of Delegates on October 15, 2014
https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system

ASA PS Classification	Definition	Examples, including but not limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

18.3. APPENDIX C: List of Investigators and Institutions

Investigational Sites information including addresses, contact information, Principal Investigators, their respective IRBs, and will be retained in a separate document from the body of the clinical investigation plan document. This will be provided to investigational sites and updated as necessary.