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.

NCT03515811

Statistical Analysis Plan, 08-MAR-2019

Medtronic	CONFIDENTIAL	DOCUMENT/RECORD

This document/record is electronically controlled; printed copies are considered uncontrolled.
System of Record: Regulatory Affairs Domain

Document Name	RAD Version
SAP v1 2019 03 11 MDT17025SIG	1.0

Title	SAP v1.0 2019 03 11

APPROVALS

Signed By	Meaning of Signature	Date/Time (UTC)
Discipio, Andrea	Clinical Research Specialist	03/11/2019 14:27:18
Lourd, Mathilde	Biostatistician	03/11/2019 14:29:02
Pace, Michael	Clinical Study Manager (CSM)	03/19/2019 17:35:09

Medtronic

Statistical Analysis Plan v1.0 [Final]

Clinical Investigation Plan 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
Clinical Investigation Plan Version	V3.0 10-Aug-2018
Sponsor/Local Sponsor	**Covidien -Medtronic** Minimally Invasive Therapies Group Surgical Innovations 15 Hampshire St Mansfield, MA, 02048 USA
Document Version	v1.0 Final (08Mar2019)

Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
[Final v1.0]	• N/A (initial release)	Mathilde Lourd, Sr Biostatistician, Corporate Biostatistics

2. List of Abbreviations and Definitions of Terms

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)

Term	Definition
CIP	Clinical Investigation Plan (can be used synonymously with Protocol)
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
IFU	Instructions for use
ISO	International Organization for Standardization
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
OLED	Organic light emitting diodes
SAE	Serious Adverse Event - Adverse event that:

Term	Definition
	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. Introduction

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.

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.

This document outlines the detailed statistical methods to be implemented for the data collected within the scope of the study. The Clinical Investigation Plan (CIP) document was used to create the Statistical Analysis Plan (SAP).

4. Study 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)

4.1. Primary Objective

The primary endpoint is the incidence of subjects reporting serious adverse device effects (SADEs) 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.

4.2. Secondary Objective

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.

5. Investigation Plan

This is a prospective, two-arm, non-comparative, multicenter, post-market study on adult subjects undergoing abdominal or thoracic procedures using Signia™ Stapling System and appropriate reloads.

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).

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). It is estimated that the abdominal arm will comprise of approximately 53 subjects and the thoracic arms comprise of approximately 74 subjects.

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. Enrolled 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.

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)

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 reload contraindications as described in the IFU, respectively.

Study procedures and assessment are described in the study schematic hereafter.

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		

Procedure/Assessment	Screening (Day -30 to 0)	Operative (Day 0)	Discharge Assessment	Follow-up Assessment (at 30 Days (+14 days))
	Can be combined			
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.
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

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.

A preliminary analysis will be conducted in the study when half-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.

6. Determination of Sample Size

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.

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

Summaries of screened, consented and enrolled subjects will be provided overall, and in each arm (Abdominal and Thoracic) separately
Overall and for each indication, subjects in the Full Analysis Set (FAS), and in Per protocol Analysis Set (PPAS) will be summarized, according to follow-up, and within each investigational site.
Reason for study discontinuation will be tabulated based on FAS.

7.1.2. Clinical Investigation Plan (CIP) Deviations

Subjects with protocol deviations will be summarized and protocol deviations will be reported by type on overall FAS subjects and distinguishing minor and major protocol deviations/violations.

Major protocol deviations and violations will be defined and identified by the study team prior to run statistical analysis, based on protocol deviations listing provided by statistician.

7.1.3. Analysis Sets

Full Analysis Set (FAS): includes 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 Analysis Set (PPAS): includes all subjects from the FAS population who do not have a major protocol violation. Analyses on the PPAS will provide supporting evidence to the primary results (obtained on FAS).

7.2. General Methodology

Statistical analysis will be descriptive, and run separately in each arm:

- 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.

Some subgroup comparative analyses may be run in addition to primary and secondary endpoints, to assess impact of demographic characteristics, risk-factors, and surgery technique on the performance and safety outcomes.

In case of comparative analysis is performed:

- Pearson Chi-square test or Exact test will be used (as appropriate) for categorical data
- Student t-test or Wilcoxon rank sum test will be used if assumptions of t-test are not verified for continuous data.

7.3. Center Pooling

The study will be conducted in a minimum of 4 investigational sites. Screening and surgical data will be summarized for overall subjects and for each site separately, to confirm homogeneity of subject's characteristics between sites.

Primary and secondary endpoint analysis will be run on overall subjects. In case of imbalance regarding subject's characteristics between sites, additionnal subgroup analyses for primary and secondary endpoints could be performed according to investigational sites.

7.4. Handling of Missing, Unused, and Spurious Data and Dropouts

No data imputation will be performed for missing data. 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.

7.5. Adjustments for Multiple Comparisons

Statistical analysis of primary endpoint is descriptive. No adjustment will be done.

7.6. Demographic and Other Baseline Characteristics

Screening and demographics characteristics, medical/surgical histories and risk-factors will be summarized using descriptive statistics.

7.7. Treatment Characteristics

For efficacy and safety endpoints assessment, some subgroup analyses may be run according to surgical technique and device caracteristics; all these characteristics may impact efficacy and safety results.

7.8. Interim Analyses

A preliminary analysis will be conducted in the study when 64 enrolled subjects complete the 30 day (+/-14days) 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.

7.9. Evaluation of Objectives

Study objectives will be assessed through study endpoints measurement.

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 analysis will be performed in abdominal group and in thoracic group, and in the combined groups, based on Full analysis Set, as defined previously. A confirmatory analysis of primary endpoint will be run using Per Protocol Analysis Set.

Secondary endpoints

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.

Secondary endpoints analysis will be run on Full Analysis Set and on Per-Protocol Analysis Set.

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.

7.10.Safety Evaluation

Safety will be assessed as the proportion of subjects with AE based on the FAS, and on PPAS. AE incidence will be reported overall, and according to:

- Relation to the procedure
- Relation to the device including anticipated and unanticipated ADEs, related to:
  - Signia Stapling device, and/or
  - Stapler reloads
- Severity,
- Seriousness.

Listing of AEs, SAEs, ADEs and SADEs, and UADEs will be provided based on FAS and PPAS, using the MEdDRA coding system classification for AE terms, and including characteristics described previously and AE outcome.

7.11. Health Outcomes Analyses

Health outcomes analyses are already part of primary and secondary endpoints analyses, as described previously.

7.12. Changes to Planned Analysis

Any major change in planned analysis as described in this SAP would result in SAP amendment.

8. Validation Requirements

Validation level I will be applied for endpoints evaluated at the interim and final analyses.

Validation level I is defined as follows: the peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer.

9. References

N/A

10. Statistical Appendices

N/A