Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	A prospective, multi-center, single-arm study of the Medtronic Hugo™ Robotic Assisted Surgery (RAS) System in Inguinal and Ventral Hernia Repair Surgery
Clinical Investigation Plan Identifier	MDT21022
Clinical Investigation Plan Version	Version 5.0, 02-Sep-2025
Statistical Analysis Plan Version Date	19-Dec-2025
Sponsor/Local Sponsor	Covidien LP, Medtronic Medical Surgical Surgical Robotics 60 Middletown Ave North Haven, CT 06473 USA

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Initial release	[redacted]
2.0	• Update referenced CIP version since CIP V4.0 was not implemented • Additional clarification on how subjects will be chosen for objectives defined for "through 30 days" • Clarification that, when available, CEC adjudication will be used for all analyses	[redacted]
3.0	• Update following CIP V5.0 ○ CEC adjudication requirements ○ Removed changes as compared to CIP V3.0 ○ Site recruitment limits	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ACHQC	Abdominal Core Health Quality Collaborative
ADE	Adverse Device Effect
AE	Adverse Event
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CIP	Clinical Investigational Plan
CSR	Clinical Study Report
DD	Device Deficiency
FAS	Full Analysis Set
FDA	Food and Drug Administration
MedDRA	Medical Dictionary for Regulatory Activities
PD	Protocol Deviation
PG	Performance Goal
PPAS	Per Protocol Analysis Set
RAS	Robotic Assisted Surgery
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SSE	Surgical-Site Event
SSI	Surgical-Site Infection
SSO	Surgical-Site Occurrence
UADE	Unanticipated Adverse Device Effect
US or USA	United States of America

3. Introduction

A hernia is a protrusion of tissue or part of an organ through bone, muscular tissue, or membrane. Inguinal hernias occur in or near the inguinal canal and ventral hernias occur in the abdomen wall. Lifetime risk for inguinal hernia occurrence is 3% for women and 27% for men. Ventral hernias occur in the abdomen wall and are sometimes referred to as abdominal hernias; sub-types of ventral hernias include incisional hernias, umbilical hernias, and epigastric hernias. The traditional treatments for hernia are open and laparoscopic surgeries. In recent years, Robotic assisted surgery emerged and has gradually been adopted as an alternative. The Medtronic Hugo™ RAS system is a modular robotic platform for performing robotic assisted minimally invasive surgery. This clinical study is designed to evaluate the safety and effectiveness of the Hugo™ RAS system for subjects in inguinal and ventral hernia repair surgery.

This statistical analysis plan (SAP) serves as a guideline for study Biostatistician(s), Statistical Programmer(s), and other stakeholders for internal use. The purpose is to provide general, and in some instances, specific guidelines from which the analysis will proceed. It was created in accordance with the clinical investigational plan (CIP) version 5.0, dated 02-Sep-2025. If the CIP is updated, this SAP will be updated if the SAP content is impacted.

Changes to the plan may become necessary as the study progresses or when the CIP needs to be updated or as other unexpected events emerge. The planned analyses identified in this document may be included in regulatory submissions and/or future manuscripts. They will also be the basis of the Primary Endpoint (30-Day) Clinical Study Report (CSR) for this study. Any post-hoc analyses, unplanned analyses, or changes to planned analyses will be clearly identified in the CSR.

4. Study Objectives

4.1 Primary Objectives

The primary objectives of this study are to demonstrate that the Medtronic Hugo™ RAS system is safe and effective when used for inguinal and ventral robotic hernia repair.

4.1.1 Primary Objective #1 (Effectiveness) Endpoint

The primary effectiveness endpoint is the surgical success rate defined as the procedure not going into conversion. Conversion is defined as the switch from the robotic-assisted approach using the Hugo™ RAS system to laparoscopic, open surgery, or use of an alternative robotic-assisted system. Procedural steps that are usually performed without robotic assistance per standard of care, including but not limited to mesh insertion, suture needle removal, or tacking, are not considered a conversion and will not contribute to the primary effectiveness endpoint.

4.1.2 Primary Objective #2 (Safety) Endpoint

The primary safety endpoint is the overall rate of subjects with one or more study procedure- and/or device-related surgical-site events (SSEs), from the first incision of the hernia repair procedure through 30 days post-procedure. SSE is defined as the following complications:

- Surgical-site occurrence (SSO):
  - Bleeding, Hemorrhage: Requiring transfusion
  - Bowel Injury
  - Bowel Obstruction
    - Note: Functional obstruction associated with general anesthesia and/or pain killer drugs (opioids) is excluded for this endpoint
  - Cellulitis
  - Epigastric Vessel Injury
  - Symptomatic Hematoma: Requiring procedural intervention
  - Symptomatic Seroma: Requiring procedural intervention
  - Symptomatic Edema: Requiring procedural intervention

  - Note: Procedural intervention is defined as percutaneous drainage, wound opening or debridement, suture excision, or mesh removal (partial or total)
- Surgical-site infection (SSI): Infection occurring where the surgery took place, including superficial, deep, and organ space infections (standardized definition developed by the CDC)

The relatedness of the SSEs being classified as "procedure- and/or device-related" may include three scenarios, all of which are included in this primary objective: (1) only procedure-related SSEs, (2) only device-related SSEs, and (3) SSEs that are both procedure- and device-related. In this study, procedure-relatedness refers to an AE that occurs due to the hernia repair procedure with the Hugo™ RAS system, and device-relatedness refers to an AE that results from the presence or performance (intended or otherwise) of the Hugo™ RAS system.

4.2 Secondary Objectives

The secondary objective of this study is to demonstrate that the Medtronic Hugo™ RAS system performs as intended when used in inguinal and ventral hernia repair robotic assisted surgery. The secondary endpoints of this study will assess the overall performance of the Medtronic Hugo™ RAS system when used for hernia repair.

4.2.1 Secondary Objective Endpoints

Secondary objectives include descriptive analyses of secondary endpoints. The following safety and performance endpoints will be summarized for the period through 30 days post-procedure (defined as 30 calendar days after the procedure) to assess the overall safety and performance of the Medtronic Hugo™ RAS system when used for hernia repair robotic assisted surgery:

- Complication rate: Overall rate of subjects with one or more procedure- and/or device-related complications (Clavien-Dindo Grade I or higher), from the first incision through 30 days post-procedure
- Major complication rate: Overall rate of subjects with one or more major procedure- and/or device-related complications (major defined here as Clavien-Dindo Grade III or higher), from the first incision through 30-days post-procedure
- Operative time: time from skin incision to skin closure
- Readmission rate through 30 days post-procedure: Admission for a direct consequence or complication associated with the treated hernia or with the surgical procedure to treat the hernia
- Reoperation rate through 30 days post-procedure: Operation for a direct consequence or complication associated with the treated hernia or with the surgical procedure to treat the hernia
- Recurrence rate through 30 days post-procedure: Clinical hernia recurrence is defined as a palpable fascial defect and/or a clinically manifested bulge within 7 cm of the original repair, exacerbated by a Valsalva maneuver during physical examination by a study investigator.

The following long-term secondary endpoint will be assessed through 2 years post-procedure in all treated subjects:

- Recurrence rate through 2 years post-procedure

  Note: Suspected hernia recurrence(s) reported by a subject, but not confirmed by an investigator, will not be considered as a clinical hernia recurrence for this endpoint, but will be reported separately as a subject-reported recurrence in the final report.

  Clinical hernia recurrence is defined as a palpable fascial defect and/or a clinically manifested bulge within 7 cm of the original repair, exacerbated by a Valsalva maneuver during physical examination by a study investigator.

4.3 Ancillary Objectives

Descriptive analyses of other pre-specified outcome measures beyond the primary and secondary objectives will be exploratory in nature and are not intended as a focus of the study for the evaluation of the study device.

The following data will be collected as applicable:

- Estimated intraoperative blood loss
- Transfusion rate through 30 days
- Hospital length of stay
- Mortality through 30 days
- Device- and/or procedure-related AEs through 2 years
- Readmission rate through 2 years: Admission for a direct consequence or complication associated with the treated hernia or with the surgical procedure to treat the hernia
- Reoperation rate through 2 years: Operation for a direct consequence or complication associated with the treated hernia or with the surgical procedure to treat the hernia
- Surgeon experience
- Pain scores at baseline, 30-days, and 3-months (Abdominal Core Health Quality Collaborative [ACHQC] questionnaire)

5. Investigation Plan

This study is a prospective, multicenter, single-arm pivotal study that will enroll 192 subjects with either an inguinal or ventral robotic hernia repair procedure using the Medtronic Hugo™ RAS system. Subjects will be followed up to two years from the index hernia repair procedure. This study will be conducted in the United States (US) with up to ten study sites. The study required procedures and follow-up consist of the following: Screening, Surgical Procedure, Hospital Discharge, and Post-Discharge Follow-Up at 30 days (±7 days), 3 months (±14 days), 1 year (±30 days) and 2 years (±30 days).

For the study to be successful, it must meet the primary effectiveness objective, which is based on combined cohorts of inguinal and ventral. The primary safety objective must be met for each corresponding hernia cohort (inguinal, ventral) independently. That is to say, the primary safety objective could be successful for one hernia cohort and failed for the other.

6. Determination of Sample Size

The sample size for the study was estimated based on the primary safety and effectiveness hypotheses.

The effectiveness hypothesis is to test if the surgical success rate is above the performance goal. The sample size for primary effectiveness is based on combined cohorts of inguinal and ventral. A performance goal of 85% (100%-conversion rate) is pre-defined to test the statistical hypothesis. Assuming a success rate of 93%, a sample size of 172 subjects for the combined inguinal and ventral hernia cohort will provide 90% of power with one-sided alpha of 0.025. Calculation was performed using the PASS 2023. Accounting for 10% attrition rate, the enrollment is 192 subjects with a hernia repair procedure.

The primary safety objective is also part of the consideration for the sample size determination. The primary safety endpoint is the rate of subjects with any procedure- and/or device-related SSEs from the first incision through 30 days post-procedure. The primary safety objective, assessed separately for each hernia cohort, is based on a performance goal of 30% and expected safety event rate of 15% for the cohort. A sample size of 86 will provide 86% power with a one-sided alpha of 0.0125 (Bonferroni Correction for hernia cohort). Calculation was performed using the PASS 2023. Accounting for 10% attrition rate, the enrollment is 96 per cohort or 192 total subjects with a hernia repair procedure.

An attrition rate of 10% was assumed to ensure an adequate sample for each objective, resulting in 192 total subjects (96 per hernia cohort).

Endpoint	Performance Goal	Expected Study Rate	Minimum Sample Size	Minimum Power	Minimum Alpha
Primary Effectiveness	85%	93%	172	90%	0.025
Primary Safety	30%	15%	86	86%	0.0125

The secondary objectives will be assessed using descriptive statistics and no sample size assessment was made for these objectives.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be illustrated in a CONSORT diagram. The number of subjects screened, treated, discontinued during the study, as well as the reasons for discontinuations will be summarized for all centers combined and each center separately. Reason for study discontinuation will also be provided as a by-subject listing.

7.1.2 Clinical Investigation Plan (CIP) Deviations

The number protocol deviations will be reported by deviation type.

7.1.3 Analysis Sets

The following populations will be considered for the analysis of data for this study. All enrolled subjects will be included in a subject disposition table indicating reasons for exclusion from each analysis set.

Enrolled Analysis Set

All subjects who signed informed consent.

Full Analysis Set

The full analysis set (FAS) is defined as all enrolled subjects in whom the Hugo™ RAS procedure is begun, defined as the first skin incision. If a subject is consented, but the first incision does not occur (e.g., if the subject becomes ineligible during the timeframe between consent and the procedure day), the subject will not be considered part of the FAS. The FAS will be the primary analysis set for the evaluation of the primary, secondary, and ancillary endpoints. In the case of missing data with no imputation, some subjects may be excluded from an objective analysis using the FAS analysis set. Consider imputation plans defined in section **7.4**.

Per Protocol Analysis Set

The per protocol analysis set (PPAS) is a subset of the FAS including only those subjects without any major protocol deviations. Major deviation reasons include “Enrolled subject did not meet enrollment criteria” and “Unauthorized use of investigational device.” Reasons for exclusion of subjects from PPAS will be documented in the CSR.

7.1.4 Assessment of Treated Hernia Type

Subjects enrolled in the study are indicated for inguinal (unilateral or bilateral) or ventral hernia (with a maximum size of <10cm). In some cases, subjects may have hernia treated in a way that is adjacent or beyond the expected items above. For example, an inguinal subject may have an unknown femoral hernia near the intended inguinal hernia; in this case, the surgeon might consider it most ethical to fix both hernia with Hugo during the single procedure. In another example, a surgeon may identify ventral hernia that require repair after starting the inguinal procedure.

For the purposes of analysis, subjects will be included with the initially intended hernia type (expected to be inguinal in most cases where multiple hernia types are treated). The main safety analyses will include all events for the subjects with the initially intended hernia type. For cases where a subject has both inguinal and ventral hernia, adverse events will be assessed to determine whether any events are related primarily to the ventral hernia; in these cases, a sensitivity analysis may be added for the primary safety objective to include this event/subject in the ventral cohort in addition to the inguinal cohort.

7.2 General Methodology

All data analyses will be performed by Medtronic or its designee. All statistical analyses will be performed using the Statistical Analysis System (SAS, version 9.4 or higher, SAS Institute Inc. Cary, NC) or other widely accepted statistical or graphical software.

Descriptive statistics will be used to summarize study outcomes. Continuous variables will be summarized using number of subjects (n), mean, standard deviation, median, 25th quartile, 75th quartile, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages.

The study safety and performance analyses related to the procedure and to data through 30 days will occur after all subjects complete the 30-day follow-up visit, discontinued prior to the visit, or were confirmed to miss the visit. A CSR will be prepared once all data collection has ended and all subjects have completed the 30-day follow-up or have exited. A final report will be completed at the end of the 2-year follow-up.

For consideration of study visits, the target number of days from the procedure to each visit is 90 days, 365 days, and 730 days for the 3-month, 1-year, and 2-year visits, respectively.

7.3 Center Pooling

Up to ten study sites will be used. To keep enrollment balanced, a single study site will be allowed to treat no more than 30% of the total population. Study centers will be pooled together for all planned analyses unless they are proven to be heterogeneous in terms of clinical practice, effectiveness and safety.

An assessment of data poolability of the sites will be performed using logistic regression with the outcome being surgery success (1=successful surgery, 0=converted surgery). A p-value of 0.15 or less will be considered significant (per FDA recommendation). Sites with fewer than five treated subjects will be combined into one larger site to ensure statistical robustness. If the sites are found to be significantly heterogeneous with respect to the primary endpoint, additional analyses will be conducted to further assess variations across sites in baseline and procedural variables that might contribute to the variation.

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

The primary effectiveness analysis will be based on the FAS. If 5% of the data or fewer are missing for the analysis, no imputation will be used (Buhi, Jakobsen). Otherwise, missing data will be imputed for the FAS using multiple imputation (MI). Unless model errors dictate otherwise, the model variables used for the MI analysis will include baseline variables age, gender (1=female, 0=male), and BMI; the model will also include a variable for hernia cohort (inguinal=1, ventral=0). Ten imputations will be conducted and combined using the Rubin's rule (Rubin) after 100 burn-in iterations. The estimate and variance of the mean proportion of subjects considered a surgical success will be determined for each imputation dataset. For the primary objective, the mean and variance for the proportion will be determined using MI analysis methods and the objective will be tested using a Z-test comparing the observed surgical success rate to the primary objective performance goal of 85%. The seed will be defined as the date of the database snapshot in the format YYYYMMDD.

Sensitivity analysis will be performed for the primary effectiveness objective using available data in both FAS and PPAS as well as tipping-point analysis in FAS to fully understand the missing data impact on the study results.

The primary safety analysis will be based on FAS subjects with available data at 30-days, i.e. whose status (event, no event) at 30-days can be determined. For the secondary and ancillary endpoints, analysis will be conducted with available data in FAS. No imputation will be conducted for these analyses. Additional clarification for determining data availability at 30 days:

- Subjects with a 30-day visit at least 30 days post-procedure have complete/available 30-day data
- For subjects whose 30-day visit occurred within the visit window between 23 and 29 days post-procedure, these subjects will be considered as have been followed through 30 days and their event status will be determined using any events that occurred through 30 days post-procedure, even if occurring after the 30-day visit
- Subjects who did not complete a 30-day visit will be considered to have available data in the following scenarios:
    - 1) if the subject completed zero follow-up visits and has a relevant event in the 30 days following the procedure, the subject will be included in the analysis as having the event;
    - 2) for subjects without a relevant event and who missed the 30-day visit but had some other post-procedure visit within the 30-day visit window or at anytime after the 30-day window (e.g., a completed 3-month visit), the subject will be included in the analysis as not experiencing the event. Visits and discontinuations after the 3-month visit will not be considered under this provision.

7.5 Adjustments for Multiple Comparisons

For the primary effectiveness endpoint, one hypothesis will be tested at an alpha of 0.025 one-sided. If the one-sided primary objective p-value is <0.025, then the null hypothesis will be rejected, and the test will be declared statistically significant.

After the primary effectiveness objective is met, the primary safety objective for each hernia cohort will be tested**.** For the primary safety endpoint (procedure- and/or device-related SSE rate), the closed test procedure (Holm's method, i.e. Holm-Bonferroni method) will be used to protect the overall study-wise error rate for hernia cohorts (inguinal hernia and ventral hernia), thereby maintaining an overall type I error of one-sided of 0.025 for these objectives. To assess statistical significance of these objectives, the one-sided p-values will be determined and ordered from smallest to largest. First, the smaller p-value will be compared to 0.0125. If the p-value is larger than 0.0125, both tests will be considered non-significant. If the smaller p-value is less than 0.0125, the test will be considered significant and the larger p-value will be assessed; the larger p-value is then assessed with a p-value below 0.025 resulting in a determination of statistical significance for the larger p-value.

Secondary objectives and ancillary objectives are intended to be descriptive only. No multiplicity adjustment will be applied.

7.6 Demographic and Other Baseline Characteristics

Demographic summaries will include age (in years), sex, race/ethnicity, and BMI.

7.7 Treatment Characteristics

A descriptive data summary for surgical procedure characteristics and exposure to the study device will be provided. Summaries will be discussed in the study report.

7.8 Interim Analyses

No interim analysis is planned for this study.

7.9 Evaluation of Objectives

7.9.1 Primary Effectiveness Objective

The primary effectiveness objective of this study is to demonstrate that the Medtronic Hugo™ RAS system is effective when used in inguinal and ventral hernia repair. The primary objective on effectiveness is to demonstrate that the surgical success rate is greater than the pre-defined performance goal (PG). The surgical success is defined as the procedure not going into conversion due to failure of the Hugo™ RAS system. Conversion is defined as the switch from the robotic-assisted approach using the Hugo™ RAS system to laparoscopic, open surgery, or use of an alternative robotic-assisted system. Procedural steps that are usually performed without robotic assistance per standard of care, including but not limited to mesh insertion, suture needle removal, or tacking, are not considered a conversion and will not contribute to the primary effectiveness endpoint.

7.9.1.1 Hypothesis

The primary effectiveness hypothesis is to test if the surgical success rate is above the performance goal. A performance goal of 85% (100% - conversion rate) is pre-defined to evaluate the surgical success rate. Let P be the surgical success rate in this study. The statistical hypothesis is as follows:

$$H_0: P \leq 85\% \quad vs. \quad H_a: P > 85\%$$

7.9.1.2 Endpoint Definition and Derivation

Sites are asked if the procedure was completed according to the surgical plan (Yes/No). If the answer was “No”, the site reported what was not done per the surgical plan; if the site specifies “Converted”, then the surgery is identified as a conversion. Surgical success is defined as a surgery that has not involved a conversion.

7.9.1.3 Performance Requirements

The null hypothesis will be rejected if the p-value for the one-sided hypothesis test is less than 0.025.

7.9.1.4 Rationale for Performance Criteria

To determine performance criteria, analyses were performed on available literature. Point estimates along with 95% and 99% predicted intervals were calculated to provide plausible ranges of potential effect sizes. Clinically meaningful margins and statistical precisions have been taken into account to determine the appropriate performance goals. The performance goal (PG) of 85% is derived on literature research (**Table 1**).

Table 1: Primary Effectiveness Endpoint – Performance Goal Determination

Primary Effectiveness Endpoint: Surgical Success Rate		
Surgery Type	**Performance goal (PG)**	**Rationale**
Inguinal and Ventral Hernia Repair	85%	The literature-based mean effect size for conversions is 1.5% with a 95% CI of 0.2% to 9.4%. The 95% prediction interval is 0.1% to 29.3%. A PG of 85% for the surgical success rate, equivalent to a 15% conversion rate, is set, which is aligned with the upper 95% CI with an added 5.6% margin and falls within the 95% prediction interval.

7.9.1.5 Analysis Methods

The surgical success rate will be calculated as the proportion of subjects with a successful surgery. The hypothesis will be tested using the binomial test at one-sided alpha of 0.025. In the case of multiple imputation, the objective will be tested using a Z-test. The 95% two-sided confidence interval will also be reported; The confidence interval will be calculated using the Clopper-Pearson exact binomial method, with Wald confidence interval provided in the case of imputation.

7.9.1.6 Determination of Subjects/Data for Analysis

The analysis set for the primary effectiveness will be the full analysis set (FAS) for the combined inguinal and ventral hernia cohort. If 5% of the data or fewer are missing for the primary analysis, no imputation will be used. Otherwise, missing data will be imputed for the FAS using multiple imputation.

7.9.1.7 Supporting Analyses

7.9.1.7.1 Sensitivity Analysis

In the case of no imputation for the primary objective, the first sensitivity analysis will use multiple imputation (MI) to impute missing outcome data (see MI details in section **7.4**). In the case of imputation, the first sensitivity analysis will use those subjects with data for the assessment.

Another sensitivity analysis will be to assess the primary objective using the PPAS, excluding subjects with major protocol deviations.

The final sensitivity analysis will be a tipping point analysis (based on the FAS) with the missing outcome data. In this analysis, missing primary outcome data will be imputed as failure to determine the proportion of subjects with missing data that would need to be converted to another form of surgery (e.g., open, laparoscopic, alternative RAS) to change the primary effectiveness endpoint conclusions.

A summary of subjects with missing data, along with reasons for missing data, will be provided.

7.9.1.7.2 Sub-group Analyses

Subgroup analysis for the primary effectiveness objective will be performed by cohort (inguinal, ventral), gender, age group (based on median age), race, and ethnicity. Sub-group analysis will be performed using FAS with available data. No imputation will be applied. Any subgroup with less than 10 subjects may not be reported.

7.9.2 Primary Safety Objectives

The primary safety objective of this study is to demonstrate that the Medtronic Hugo™ RAS system is safe when used in inguinal and ventral hernia repair. The primary objective on safety is to demonstrate that the surgical site event rate is less than the pre-defined performance goal (PG). The primary safety endpoint is the rate of subjects with one or more procedure- and/or device-related SSEs from the first incision through 30 days post-procedure.

7.9.2.1 Hypothesis

The primary safety hypothesis is to test the overall 30-day procedure- and/or device-related SSEs rate (i.e., rate of subjects with one of more procedure- and/or device-related SSEs) against a performance goal for each hernia cohort. A performance goal of 30% is pre-defined to evaluate the SSE rate. Let *R* be the 30-day procedure- and/or device-related SSEs rate for each specific hernia cohort. The statistical hypothesis is formulated as follows for each hernia cohort:

$$H_0: R \geq 30\% \quad vs. \quad H_a: R < 30\%$$

7.9.2.2 Endpoint Definition and Derivation

The rate of SSE within 30 days is calculated as the proportion of subjects who experience an SSE during the procedure and through 30 days after the procedure. SSE are defined in detail in section **4.1.2**. The AE start date of the adverse event will be used to determine when an SSE was experienced.

7.9.2.3 Performance Requirements

Each null hypothesis will be rejected if the p-value for the one-sided hypothesis test is less than the multiplicity-adjusted alpha as described in Section **7.5** (Holm's method, i.e. Holm-Bonferroni method).

7.9.2.4 Rationale for Performance Criteria

A literature search was performed for each of the surgery types (inguinal hernia repair and ventral hernia repair) including RAS and laparoscopic procedure types. Point estimates along with 95% confidence intervals (CIs) and prediction intervals were calculated based on the reported literature data. Clinically meaningful margins and statistical precisions have been considered to determine the appropriate performance goals. The performance goals (PG) of 30% are derived on literature research (**Table 2**).

Table 2: Primary Safety Endpoint – Performance Goal Determination

Primary Safety Endpoint: Rate of Subjects with One or More Procedure-/Device-Related Surgical Site Events (SSEs) through 30 Days Post-Procedure		
Surgery Type	**Performance Goal (PG)**	**Rationale**
Inguinal Hernia	30%	The literature-based maximum possible SSE rate is 3.8% with a 95% CI of 2.1% to 6.9%. The 95% prediction interval is 0.3% to 36.0%. A PG of 30% falls within the 95% literature-based prediction interval and is clinically relevant.
Ventral Hernia	30%	The literature-based maximum possible SSE rate is 4.5% with a 95% CI of 1.8% to 10.8%. The 95% prediction interval is 0.3% to 45.5%. A PG of 30% falls within the 95% literature-based prediction interval and is clinically relevant. Additionally, Medtronic-sponsored clinical study data show a 14.5% procedure- and/or device-related SSI + SSO pooled rate, with a 95% CI of 8.8% to 22.0%. With an approximate 8% clinical margin added to the upper 95% confidence bound, these data support the PG of 30%.

7.9.2.5 Analysis Methods

The proportion of subjects experiencing SSE in each hernia cohort will be reported and compared against the performance goals using the binomial test. The proportion of subjects experiencing the component of SSE, i.e. SSO and SSI, will also be reported. The 95% two-sided confidence interval will be reported using the Clopper-Pearson exact binomial method.

7.9.2.6 Determination of Subjects/Data for Analysis

The analysis set for the primary safety objective will be FAS with available data at 30 days, i.e., those subjects whose status (event, no event) at 30 days can be determined. Data availability for assessments through 30 days will follow the logic described in section **7.4**. The inguinal hernia cohort and ventral hernia cohort will be analysed separately.

7.9.3 Secondary Objectives

The secondary objectives of this study are to demonstrate the Medtronic Hugo™ RAS system performs as intended when used in inguinal and ventral hernia repair. The secondary endpoints of this study will assess the overall performance of the Medtronic Hugo™ RAS system when used for the robotic surgery.

The role of the secondary endpoints is to explore additional effects and outcomes associated with either the procedure or the disease state. The pre-specified performance goals serve as benchmarks for interpretation rather than thresholds for statistical significance of clinical trial success in this study.

Statistical evaluations for secondary objectives with performance goals are not powered in this study. Therefore, the secondary endpoints are planned to be analyzed descriptively with no plans for statistical

testing. Secondary objectives will be analyzed using all subjects from whom data is available. Data availability for assessments through 30 days will follow the logic described in section **7.4**.

7.9.3.1 Objectives, Endpoint Definitions and Derivations

Endpoint	Endpoint Definition and Derivation
Any complication rate through 30 days post procedure	Overall rate of subjects with one or more procedure- and/or device-related complications (Clavien-Dindo Grade I or higher), from the first incision through 30 days post-procedure. CD Grade and device and/or procedure relatedness is assessed by the study site. Where CEC assessment of device and/or procedure relatedness is available, it will be used as the primary source of relatedness.
Major complication rate through 30 days post procedure	Overall rate of subjects with one or more major procedure- and/or device-related complications (Clavien-Dindo Grade III or higher), from the first incision through 30-days post-procedure. CD Grade and device and/or procedure relatedness is assessed by the study site. Where CEC assessment of device and/or procedure relatedness is available, it will be used as the primary source of relatedness.
Operative time	Time from skin incision to skin closure. This will also be summarized separately for the following: • Unilateral operative time for inguinal hernia • Bilateral operative time for inguinal hernia • Operative time for ventral hernia
Readmission rate through 30 days post procedure	Admission for a direct consequence or complication associated with the treated hernia or with the surgical procedure to treat the hernia. A readmission is determined by the study site on the AE CRF.
Reoperation rate through 30 days post procedure	Operation for a direct consequence or complication associated with the treated hernia or with the surgical procedure to treat the hernia. A reoperation is determined by the study site on the AE CRF.
Recurrence rate through 30 days post procedure	Clinical hernia recurrence is defined as a palpable fascial defect and/or a clinically manifested bulge within 7 cm of the original repair, exacerbated by a Valsalva maneuver during physical examination by a study investigator. A recurrence is determined by the study site on the AE CRF. Only confirmed recurrence will be included in this rate. Secondary hernias will be differentiated from primary hernia recurrences by the study investigator. Secondary hernias are defined as a hernia located >7 cm of the original hernia repair. Secondary hernias will be excluded from hernia recurrence reporting for all hernia recurrence endpoints.
Recurrence rate through 2 years post procedure	This analysis uses similar definitions as recurrence rate through 30 days. Note: Suspected hernia recurrence(s) reported by a subject, but not confirmed by an investigator, will not be considered as a clinical hernia recurrence for this endpoint, but will be reported separately as a subject-reported recurrence in the final report.

7.9.3.2 Hypotheses

The secondary objectives are not powered in this study. Instead, the secondary endpoints will be analyzed using descriptive statistics, which broadly negate the need for multiplicity adjustments.

7.9.3.3 Performance Requirements

The role of the secondary endpoints is to explore additional effects and outcomes associated with either the procedure or the disease state. The pre-specified performance goals (also referred as performance targets for the secondary objectives) serve as benchmarks for interpretation rather than thresholds for statistical significance of clinical trial success in this study.

Performance targets for each of the secondary objectives can be found in the CIP.

7.9.3.4 Analysis Methods

Descriptive statistics will be provided as defined in section **7.2**.

7.9.3.5 Determination of Subjects/Data for Analysis

The analysis set for the secondary objectives will be the FAS with available data. Data availability for assessments through 30 days will follow the logic described in section **7.4**. The secondary endpoints will be analyzed for the inguinal and ventral hernia cohorts separately and when combined.

7.9.4 Ancillary Objectives

Descriptive analyses of ancillary objectives will be exploratory in nature and are not intended as a focus of the study for the evaluation of the study device.

Endpoint	Endpoint Definition and Derivation
Estimated intraoperative blood loss	Estimated blood loss is assessed by the study site on the Procedure CRF.
Transfusion rate through 30 days	Use of transfusion was assessed by the study site on the AE CRF.
Mortality through 30 days	Death is assessed by the study site on the AE and Exit CRFs.
Device- and/or procedure-related AEs through 2 years	The CEC assessment of device and/or procedure related will be used as the primary source of relatedness. For events without CEC adjudication, the study site assessment will be used from the AE CRF.
Hospital length of stay	Hospital length of stay is determined from the start of the procedure (first incision) and discharge time/date assessed by the study site on the Procedure CRF.
Readmission rate through 2 years post procedure	Admission for a direct consequence or complication associated with the treated hernia or with the surgical procedure to treat the hernia. A readmission is determined by the study site on the AE CRF.

Reoperation rate through 2 years post procedure	Operation for a direct consequence or complication associated with the treated hernia or with the surgical procedure to treat the hernia. A reoperation is determined by the study site on the AE CRF.
Surgeon experience	Surgeon experience is recorded by each surgeon after their 1st procedure and after their 10th/last procedure. These are recorded on the Surgeon_ex CRF and will be assessed by visit.
Pain scores at baseline, 30-days, and 3-months (Abdominal Core Health Quality Collaborative [ACHQC] questionnaire)	Pain scores were assessed by study subjects on the ACHQC questionnaire at baseline, 30-days, and 3-months. Summaries of the data will include worst and average pain in the last 7 days as well as current pain at the time of the assessment.

The analysis set for these ancillary objectives will be the FAS with available data. Data availability for assessments through 30 days will follow the logic described in section **7.4**. The ancillary endpoints will be analyzed for the inguinal and ventral hernia cohort respectively.

7.10 Safety Evaluation

Additional summaries of safety will be assessed for the FAS population. These include summaries of adverse events and device deficiencies (DD). AEs and DDs will be summarized with number of events, number of subjects who experienced the event, and percentage of subjects who experienced one or more events.

AEs for all subjects will be collected from consent through the study exit. AEs and DDs will be coded and summarized using the most recent version of Medical Dictionary for Regulatory Affairs (MedDRA). Serious Adverse Events (SAE), deaths, and Surgical Site Events (SSEs) will be adjudicated by an independent CEC as defined in the CIP. Cases where the investigator's classification does not match CEC's adjudication classification, both determinations will be provided within the final report; however, the CEC's adjudication will be used for data analysis.

AEs occurring in subjects excluded from the FAS will be followed post-consent through study exit and will be reported in in the CSR. These AEs will not be included in the FAS summary analysis for either AE reporting or the analysis of the primary and secondary endpoints.

For the FAS, AEs will be reported by the type (preferred term), seriousness, and procedure/device relatedness. Summaries will focus on the time periods which are complete as of the snapshot for the report, with special attention to those periods which start during the procedure (e.g. during the procedure to 30 days after the procedure).

7.11 Changes to Planned Analysis

There were no changes to the statistical analysis as compared to CIP V5.0.

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8. Validation Requirements

The analysis of the primary objectives will be validated by Level I, in which the peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer. The analysis of the secondary and ancillary objectives, as well as the main AE/PD summaries will be validated by at least Level II, in which the peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output.

9. References

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