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Document Name	RAD Version
Hello Hugo Statistical Analysis Plan v2.0.pdf	1.0

Title	Hello Hugo Statistical Analysis Plan v2.0.pdf

APPROVALS

Signed By	Meaning of Signature	Date/Time (UTC)
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Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	A prospective, single-center, single-arm, pivotal trial to evaluate safety and effectiveness of the Medtronic Hugo™ Robotic Assisted Surgery (RAS) system in prostatectomy or cholecystectomy
Clinical Investigation Plan Identifier	MDT21028
Clinical Investigation Plan Version	V6.0
Statistical Analysis Plan Version Date	26-APR-2023
Sponsor/Local Sponsor	Medtronic Korea Ltd. Glass Tower, 17F, 534 Teheran-ro, Gangnam-gu, Seoul, Korea 06181

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• N/A (initial release)	Sylvain Anselme, Sr Biostatistician, Global Clinical Data Solutions
2.0	• Remove of "The Clopper-Pearson Exact test for single proportion will be conducted." For primary and secondary endpoints	Sylvain Anselme, Sr Biostatistician, Global Clinical Data Solutions

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
DD	Device deficiency
FAS	Full Analysis Set
PPS	Per Protocol Set
RAS	Robot-Assisted Surgery

3. Introduction

Laparoscopic surgery, has the advantage of less pain and shorter hospital stay compared to open surgery as it enables to minimize incision length. However, laparoscopic approach has drawbacks such as limited field of view, weak feeling of contact, and learning curve for surgeons. Advancement in medical technology such as robot-assisted surgery (RAS) empowered surgeon to overcome these challenges, with 3-dimensional vision and better movements with improved degrees of freedom, during operational procedure **[1].** The safety and performance of commercially available RAS systems have been evaluated in previous literature showing that robotic-assisted surgery was comparable or superior to open or traditional laparoscopic surgery in terms of length of hospital stay, complication rate, intraoperative blood loss, and intraoperative conversion rate.
In Korea, the first robotic surgery was performed in 2005 and several robotic surgery devices (e.g., da Vinci® Surgical System, Revo-i) are commercially available. According to National Evidence-based Healthcare Collaborating Agency report in 2010, robotic assisted surgery has been widely performed in urological procedures (e.g., prostatectomy, nephrectomy, cystectomy, etc.) and general surgery procedures (e.g., cholecystectomy, gastrectomy, colectomy). As of 2018, annual robotic procedure volume was 20,000 cases **[2, 3].**

The Medtronic Hugo™ RAS System is a modular robotic platform for performing robotically assisted minimally invasive surgery. Preclinical studies demonstrate that the Hugo™ RAS Platform performs as intended when used for partial nephrectomy, radical prostatectomy (pelvic lymphadenectomy), radical cystectomy (ureteroneocystostomy), and radical hysterectomy/myomectomy (ovariohysterectomy).

4. Study Objectives

This study aims to evaluate the safety and effectiveness of the Medtronic Hugo™ RAS System when used on overall subjects and according to prostatectomy or cholecystectomy surgeries.

5. Investigation Plan

This study is a prospective, single-center, single-arm, pivotal trial in 40 patients undergoing prostatectomy (20) or cholecystectomy (20) using the Medtronic Hugo™ RAS System. Subjects will be followed for 30 days post procedure. As this study is a single-arm trial, no randomization or blinding will be applied. No interim analyses are planned for this study.

6. Determination of Sample Size

To estimate the number of sample size, two things are taken into account: The number of subjects from previous studies, and the minimum number[5] **[4]** to show whether the primary objective is met. We plan to include 40 patients for the study.
- Research hypotheses: The completion rate is greater than or equal to 95% (point estimate).
The completion is defined that surgery completion without conversion (to laparoscopic or open surgery) due to system serious malfunction, and without any major complications within 24-hour post-surgery. Therefore, when a subject who inevitably converted not due to the Hugo™ RAS system, it is not considered as a surgery failure as per the definition and the subject will be excluded from the primary endpoint analysis. Also, a complication within 24-hour post-surgery will not be considered as a surgery failure unless it falls under the definition of major complication.
According to previous literature on adverse events in robotic surgeries over 14 years using da Vinci, the average rates of device malfunctions and failure-related conversions was 3% (varied between 0.4% and 8.0%) and 0.9% (varied between 0.1% and 2.7%), respectively **[5].** In Korea, the reported rate of system malfunctions and failures was less than 2% among over 10,000 da Vinci robotic procedure cases between 2005 to 2013. However, no cases of malfunction led to conversion to open or laparoscopic surgery **[6].**

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Summaries of screened, consented and enrolled subjects will be provided overall.
Subjects in the Full Analysis Set (FAS), and in Per Protocol Set (PPS) will be summarized, according to follow-up, within each investigational site or within each procedure type.

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

The following populations will be considered for the analysis of data for this study:

- Full Analysis Set (FAS): The Full Analysis Set is defined as all enrolled subjects in whom the Hugo™ RAS procedure is begun (defined as the first skin incision). In the event that 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), that subject will be excluded. Also, a subject who inevitably converted (to open or conventional laparoscopic surgery) not due to the Hugo™ RAS system will be included in the safety and other descriptive analyses but excluded from the primary endpoint analysis (since the subject is not evaluable).

- Per Protocol Set (PPS): The per protocol set is a subset of the FAS including only those without any major protocol deviations. Following subjects from the FAS will be excluded from the PPS:
  - Subject who inevitably converted (to open or conventional laparoscopic surgery) not due to the Hugo™ RAS system
  - Subject did not meet Inclusion/exclusion criteria
  - Subject chooses to withdraw
  - Failure to collect required study data up to 30-day post-surgery

The FAS will be the primary analysis set for the evaluation of the primary and secondary endpoints. Statistical analysis will be performed for each analysis set. However, if all subjects complete the study per the CIP, the results can be presented regardless of the analysis set.
Subject disposition will be illustrated in a CONSORT diagram. All enrolled subjects will be included in a subject disposition table indicating reasons for exclusion from the FAS and PPS analysis sets.

7.2 General Methodology

Descriptive statistics will be used to present the data and to summarize the results. Continuous variables will be summarized with number of subjects (n), mean, standard deviation, median, and ranges. Categorical variables will be summarized by frequencies and percentages. The 95% confidence intervals for means and/or percentages will be also presented.

Statistical analyses will be presented on Overall Subjects and according to surgeries (prostatectomy, cholecystectomy).

Subgroup analyses may be used to explore the safety and performance of the study device given various patient, medical, and procedural factors. Subgroup factors include below but not limited to:

- Sex (Male vs. Female) (Cholecystectomy only)

- Age group
- ASA class
- Obesity (BMI <25 kg/m^2 vs. BMI ≥25 and <30 kg/m^2 vs. BMI ≥30 kg/m^2)
- Comorbidities (Yes vs. No)
- Procedure-specific characteristics (e.g., nerve-sparing in prostatectomy)

The following statistical tests will be used to compare each group:
- Pearson Chi-square test or Exact test will be used (as appropriate) for categorical data.
- Student t-test or Mann-Whitney test will be used if assumptions or t-test are not verified for continuous data.

7.3 Center Pooling

This study is performed in only one center.

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

Missing data will not be imputed for the primary analysis, and multiple testing adjustments are not considered. Sensitivity analysis (e.g., multiple imputations for missing data) may be performed to ensure the study results are robust.

7.5 Adjustments for Multiple Comparisons

Statistical analysis of primary and secondary endpoints is descriptive. No adjustment will be done.

7.6 Demographic and Other Baseline Characteristics

Screening and demographics characteristics, medical and surgical histories will be summarized using descriptive statistics.

7.7 Treatment Characteristics

Statistical analyses will be performed on overall operated subjects and according to subjects operated for prostatectomy and cholecystectomy.

7.8 Interim Analyses

No interim analyses are planned for this study.

7.9 Evaluation of Objectives

Study objectives will be assessed through study endpoints measurement.

- Primary Endpoint

The primary objective is to confirm that the Medtronic Hugo™ RAS System performs as intended when used for prostatectomy or cholecystectomy. Primary endpoint is below:

• Completion rate: A proportion of subjects who completed the surgery without conversion (to open or conventional laparoscopic surgery) due to system serious malfunction, and without any major complications within 24-hour post-surgery (Major complication is defined as Clavien-Dindo grade ≥3)

The number of subjects successfully completed the surgical procedure, percentage, and its Clopper-Pearson Exact 95% confidence interval will be summarized. If the point estimate of the completion rate is greater than or equal to the pre-determined value (i.e., 0.95), it is considered that the primary objective is met. This primary endpoint will be assessed on overall subjects and according to surgery performed (prostatectomy and cholecystectomy).

- Secondary Endpoints

The secondary objective is to assess the short-term safety outcome of the Medtronic Hugo™ RAS System when used for prostatectomy or cholecystectomy. Secondary endpoints are below:

- Overall complication rate through 30-day post-surgery: A proportion of subjects with any postoperative complication within 30-days post-surgery using the investigational device
- Major complication rate through 30-day post-surgery: A proportion of subjects with any postoperative complication classified ≥3 by the Clavien-Dindo system within 30-days post-surgery using the investigational device
- Readmission rate through 30-day post-surgery: A proportion of subjects hospitalized within 30 days post-surgery
- Reoperation rate through 30-day post-surgery: A proportion of subjects go through reoperation for the same indication within 30 days post-surgery
- Device deficiency rate: A proportion of subjects with any device deficiency (DD) during robotic assisted surgery using the investigational device

Descriptive statistics will be used. Frequency, percentage, and its 95% confidence interval will be presented for each secondary endpoint: overall complication rate through 30-day post-surgery, major complication rate through 30-day post-surgery, readmission rate through 30-day post-surgery, reoperation through 30-day post-surgery, and Device Deficiencies (DD) rate. The Clopper-Pearson Exact test with 95% confidence interval for single proportion will be conducted.

Secondary endpoints will be assessed on overall subjects and according to surgery performed (prostatectomy and cholecystectomy).

Any post-operative complication or major complication will be summarized by MedDRA term (system organ class and preferred term), along with the number of events and the number of subjects with an event. Regarding DD, the number of DDs and the number of subjects with a DD shall be presented.

7.10 Safety Evaluation

Safety will be assessed as the proportion of subjects with Adverse Events (AE) based on the FAS and count of AEs. incidence will be reported overall, and according to:

- Severity
- Seriousness
- Relation to the device
- Relation to the procedure
- Adverse Device Effects (Serious and Non-Serious Procedure and/or Device Related AEs)
- Serious Adverse Device Effects (Serious Procedure and/or Device Related AEs)

Listings of AEs by MedDRA terms and Death will be presented.

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 primary and secondary endpoints.

9. References

1. Lanfranco AR, Castellanos AE, Desai JP, Meyers WC. Robotic Surgery: A Current Perspective. Ann Surg. 2004;239(1):14-21.
2. National Evidence-based Healthcare Collaborating Agency. A Health Technology Assessment of the Effectiveness And Safety Of Robot Surgery. 2011.
3. Health Insurance Review and Assessment Service. Health Insurance Coverage for Robotic Assisted Surgery: A Case Study. 2019.
4. Devore J. Probability and Statistics for Engineering and the Sciences. 8th ed. Boston: Cengage Learning; 2015.
5. Koh DH, Jang WS, Park JW, et al. Efficacy and Safety of Robotic Procedures Performed Using the da Vinci Robotic Surgical System at a Single Institute in Korea: Experience with 10000 Cases. Yonsei Med J. 2018;59(8):975-981.
6. Alemzadeh H, Raman J, Leveson N, et al. Adverse Events in Robotic Surgery: A Retrospective Study of 14 Years of FDA Data. PLoS One. 2016;11(4):e0151470.

Summary of Changes

Version	Effective Date	Summary of Changes	Change Author
1.0	01FEB2023	Initial Release	Sylvain Anselme
2.0	26APR2023	alignment with OU Biostats team for performance goal	Sylvain Anselme