Product Surveillance Registry (PSR)
Surgical Statistical Analysis Plan Version 1.0
16-Aug-2021
NCT05095935

Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	Product Surveillance Registry (PSR) Surgical Platform Base CIP
Clinical Investigation Plan Version	Version 2, Comprised of: ○ PSR Core Version 9 ○ Surgical Appendix Version 2
Sponsor/Local Sponsor	Medtronic, Inc. Operational Headquarters 710 Medtronic Parkway Fridley, MN 55432 USA Covidien LP/Medtronic, Inc. Minimally Invasive Therapies Group 5920 Longbow Drive Boulder, CO 80301 USA

Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not Applicable, New Document	Lei Zhang, Prin. Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AD	Addendum
ADaM	Analysis Dataset Model
ADE	Adverse Device Effect
AE	Adverse Event
AP	Analysis Plan
CER	Clinical Evaluation Report
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRF	Case Report Form
DD	Device Deficiency
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
IC	Informed Consent
ICF	Informed Consent Form
IRB	Institutional Review Board
LAR	Legally Authorized Representative
MedDRA	Medical Dictionary for Regulatory Affairs
PI	Principal Investigator
PAS	Post-Approval Study
PSR	Product Surveillance Registry
SADE	Serious Adverse Device Effect
SD	Standard Deviation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI	Surgical Innovations
SR	Surgical Robotics
TLG	Tables, Listings and Graphs

3. Introduction

In 2011, Medtronic launched the global Product Surveillance Registry (PSR). It was built on more than 25 years of post-market clinical surveillance experience and designed to provide continuing evaluation and periodic reporting of safety and effectiveness of market-released products for their intended use.

Data collected in the PSR supports post-market surveillance activities and post-approval studies initiated by Medtronic, regulated by local governments, or conducted to fulfill government and/or regulatory

authority requests. The PSR also obtains clinical evidence to guide the development and improvement of medical devices, therapies, device guidelines, patient services/solutions and provide clinical data to support health economics and clinical outcomes research.

The PSR supports multiple Medtronic Surgical Innovations (SI) and Surgical Robotics (SR) products used in a wide range of surgical and medical procedures including minimally invasive procedures, robotic procedures, endoscopic procedures, and percutaneous procedures.

This Statistical Analysis Plan (SAP) is designed to document, before data is analyzed, the planned statistical analyses, and to support regulatory reports and *ad hoc* data requests. Reports generated using the PSR data may not contain all the objectives described below; however, if a report contains an objective outlined within this document, the analysis of that objective will be performed as described in this SAP. If additional analyses are required but not covered in this SAP, a study specific SAP addendum may be developed. A thorough explanation and rationale for any analyses conducted differently than outlined in the PSR Surgical Platform Base Clinical Investigation Plan (CIP) or SAP will be provided in conjunction with the analyses/output.

The following document was used to create this SAP: Product Surveillance Registry Platform Base Clinical Investigation Plan, Version 9, 19 May 2020 and its Surgical Appendix, Version 2, 07 Dec 2020.

4. Study Objectives

The objective of PSR Surgical Platform is to serve as an ongoing source of product performance, patient safety and clinical outcomes information associated with the use of market released Medtronic products for surgical innovations and surgical robotics.

4.1 Primary Objective

The primary objective is to evaluate the safety and performance of Medtronic market released products for surgical innovations and surgical robotics. The objectives include, but are not limit to the following:

- To estimate the surgical or medical procedure related and/or the product related event rate
- To characterize the surgical or medical procedure related events and/or the product related events

Depending on the products, the primary endpoint may be assessed at different time point, e.g. after procedure, 30-day post procedure, or 5 years post procedure. For details, please refer to the study protocol.

4.2 Secondary Objective

The secondary objectives are intended to gain additional information about safety and performance of the products for surgical innovations and surgical robotics. There are no established performance goals related to the secondary objectives.

For products following the short-term schedule, the following variables/outcomes will be evaluated to gain additional information, but are not limited to:

- Procedure details including intra- and post-operative assessments
- Incidence of specific events during or post procedure

- Mortality
- Length of hospital stay
- Readmission rate
- Reintervention rate
- Product related events
- Device deficiencies (DD)

For products following the long-term schedule, in addition to the variables/outcomes listed above, the overall survival, study-specific survivals may be carried out for safety and performance evaluation.

This SAP intends to cover the objectives specified above. For any objectives described in the study protocol or addendum, but not listed here, they will be included in study-specific SAP addendum. Please refer to study-specific SAP for the details regarding primary and secondary objectives if they are not included in this SAP.

5. Investigation Plan

5.1 Study Design

The PSR is designed to conduct active prospective post-market surveillance. Its extensible design allows products to be easily added following market release. Only subjects treated with an eligible product can be enrolled. Data collection is intended to align with routine clinical care practice.

The PSR Platform Base CIP format has a modular design which provides a framework for the collection of surveillance data to support Medtronic's product portfolio. The PSR Platform Base CIP for a given Condition/Therapy is comprised of the following:

- PSR Core: defines elements applicable to all PSR subjects, products, conditions, or therapies
- PSR Condition/Therapy Appendix: expands on the content of the PSR Core to further define specific procedure and data collection requirements for a given Condition/Therapy and is intended to align with routine care practices

PSR Surgical Platform base CIP includes PSR Platform Base CIP and its Surgical Appendix. Specific analysis requirements for each study are documented, as applicable, and are integrated with the CIP in one of two ways, either via an associated Analysis Plan (AP) or Addendum (AD). This SAP intents to cover most common objectives described in the above documents and provides statistical analysis details. In case any of the objectives or specific analysis is not covered, they will be included in SAP addendum. Together, this SAP and its SAP addendum comprise the study-specific SAP.

5.2 Duration

Overall, the PSR has no anticipated end date. However, for each individual study, the duration is determined by multiple factors, such as objectives and enrollment. It varies from study to study.

5.3 Study Population

Subjects treated with an eligible Medtronic market released surgical product(s) and enrolled within the enrollment window are eligible to participate in the PSR with additional inclusion/exclusion criteria listed below. Not all Medtronic market released surgical products are required to be included into the PSR Surgical platform. Product eligibility is based on the determination that there is an interest or requirement for obtaining additional information to further characterize product performance following market release.

5.4 Eligibility

5.4.1 Inclusion Criteria

- Subject or legally authorized representative (LAR) provides authorization and/or consent per institution and geographical requirements
- Subject has, or is intended to receive or be treated with, an eligible Medtronic surgical product
- Subject is consented within the enrollment window of the therapy received, as applicable

5.4.2 Exclusion Criteria

- Subject who is, or is expected to be, inaccessible for follow-up
- Subject is excluded by local law
- Subject is currently enrolled in, or plans to enroll in, any concurrent drug/device study that may confound the PSR results (i.e. no required intervention that could affect interpretation of all-around product safety and/or effectiveness)

Additional criteria may be required, refer to Condition/Therapy Appendix for further guidance.

6. Determination of Sample Size

The sample size calculation is based on the primary objective and serves to ensure sufficient precision for characterization of product performance. The exact definition of sufficient precision will vary based on the intended use of the data and product type. The general concept is that sample sizes should be large enough to generate meaningful estimates for population parameters of interest.

6.1 Sample size determination for event rate

To estimate sample size based on event rate and its pre-defined 95% confidence interval (CI), binomial distribution will be used. Assuming the event rate is $\hat{p}$, the sample size, *N* is estimated using the following expression (Rosner).

$$N = \frac{1.96^2 \times \hat{p}[1-\hat{p}]}{(halfwidth)^2}$$

where *halfwidth* is half of the 95% CI width. The table below shows the sample size estimates when the event rate is ranged from 5% to 20% and halfwidth is from 5% to 10%.

Event Rate \ Halfwidth	5%	7.5%	10%
5%	73	-	-
10%	139	62	-
15%	196	88	49
20%	246	110	62

6.2 Sample size for characterization of events of interest

To characterize the surgical or medical procedure related and/or the product related events, the sample size should be large enough to ensure at least one event observed with high probability, e.g. >90%, if the event rate has been reported. Otherwise, a sample size of 20-50 is recommended to provide a reasonable estimate.

The actual enrollment size for different products may vary due to regulatory requirements, sale volumes, attrition rates and manufacturing changes, etc. Enrollment will continue until a sufficient sample size is achieved to assess product performance. This sample based on Registry enrollments is representative of the worldwide population, and therefore the estimates shown should be representative of the worldwide performance of these models.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

A subject is enrolled in the study when he/she signs and dates the Informed Consent, unless a full waiver of consent has been approved by the site's IRB or EC, meets all the inclusion/exclusion criteria, and is treated with at least one eligible Medtronic market released surgical product. A flow chart, tables, and/or listings may be used to summarize subjects' disposition.

7.1.2 Clinical Investigation Plan (CIP) Deviations

If applicable, protocol deviations will be summarized by deviation type using counts and percentages.

7.1.3 Analysis Sets

Subjects included in any analysis sets must consent to the PSR, unless a full waiver of consent has been approved by the site's IRB or EC, and meet all the inclusion/exclusion criteria. They must have been treated with at least one Medtronic market released surgical product. Additional inclusion/exclusion criteria include, but are not limited to specific components or models, time frame, data cutoff date and geography. For details, please refer to Analysis Plan (AP) or Addendum (AD).

7.2 General Methodology

Descriptive summaries, unless otherwise noted, will include the number of subjects (n), mean, standard deviation (SD), minimum, 25th percentile (1st quartile), 50th percentile (median), 75th percentile (3rd quartile), maximum for continuous variables, and the number and percentage for categorical variables. Mean and percentiles will be presented to one more decimal place and SD will be presented to two more decimal places than the significant digits with which the data was collected. Minimum and

maximum will be presented to the significant digits with which the data was collected. Percentage will be displayed with one or more decimal places as appropriate. For zero count, no percentage will be presented. Exception may be applied to meet specific requirements.

7.2.1 Date format

Format all dates in reports as DD-MMM-YYYY, unless otherwise specified.

7.3 Center Pooling

Sites must meet pre-defined criteria to be selected to participate in the registry. The following methods may be incorporated to further minimize potential bias:

- Sites will consider enrollment of all eligible subjects
- Enrollment may be limited at a site level by product and/or by therapy
- Events may be adjudicated by an independent review committee, as determined by therapy or regulatory requirements
- Diverse geographical site representation
- Sites represent various types of practice settings including university, community, public and private
- Data may be assessed by an independent reviewer (e.g., Core lab) as determined by therapy
- Procedures and data collection requirements are standardized

There is no restriction on individual site enrollments as a percent of the total enrollments. However, Medtronic reserves the right to limit or close enrollment at a specific site to minimize potential bias. Data from all the study sites will be pooled for the primary analysis. Descriptive summary may be provided by study site. If substantial center heterogeneity is present, exploratory analysis may be performed to help understand the variation and evaluate the impact on the primary objective.

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

The analysis will be based on all observed data. If appropriate, missing data will be imputed per study specific SAP addendum. Data will be cleaned throughout the study, and there is no plan to exclude spurious data.

7.5 Adjustments for Multiple Comparisons

No adjustments for multiple comparisons will be made. If it is needed, details will be provided in study specific SAP addendum.

7.6 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized at subject level. Baseline is defined as the last measurements prior to surgical or medical procedure. All the variables will be summarized overall and/or by group if applicable.

Summaries of continuous variables will present n, mean, median, 25th and 75th percentiles, SD, minimum and maximum. Summaries of categorical variables will present counts and percentages. Any missing data will be excluded from the corresponding summaries, and number of missing data will be reported.

7.6.1 Demographics

Demographic variables include but are not limited to

- Age at enrollment
- Gender
- BMI (kg/m^2)

7.6.2 Baseline Characteristics

Baseline characteristics include but are not limited to:

- Medical history
- Reason for surgical or medical procedure

7.7 Procedural Characteristics

Procedural characteristics will be summarized if applicable.

7.8 Interim Analyses

Interim analysis will be completed as needed.

7.9 Evaluation of Objectives

7.9.1 Primary Objective

The primary objective is to evaluate the safety and performance of Medtronic market released products for surgical innovations and surgical robotics.

7.9.1.1 Hypothesis

No specified hypotheses for this objective.

7.9.1.2 Endpoint definition

The safety and performance of Medtronic market released surgical products is evaluated by the surgical or medical procedure related and/or the product related event rate. Depending on the follow-up schedule, the time for assessing the event rate varies. For products following the short-term schedule, the event rate is assessed post procedure or within 30 days post-procedure; for products following the long-term schedule, the time point for event rate assessment depends on the products.

In the case report form (CRF), the relatedness is collected as 4 categories: not related, possible, probable, and causal. For the primary endpoint, events classified as, 'possible', 'probable', 'causal' are considered related.

7.9.1.3 Analysis Method

Event rate is calculated as number of events divided by number of units (e.g. subjects or product uses) where events are evaluated among subjects who have enrolled, met all the inclusion/exclusion criteria, and underwent surgical procedure. If there are more than one event per unit, only the first event is relevant to the primary objective.

Two-sided 95% confidence interval (CI) of the event rate will be calculated using Binomial distribution. All the events will be summarized in a table by Medical Dictionary for Regulatory Affairs (MedDRA)

terms. The number of events, and the number and percentage of subjects who experienced the event will be reported. Surgical or medical procedure related events and/or the product related events will be listed.

7.9.2 Secondary Objective

The secondary objectives are intended to gain additional information about the safety and performance of surgical products. There will be no established performance goals related to the secondary objectives.

All the variables included in the secondary objective will be summarized overall and/or by group if applicable using descriptive statistics. For survival outcomes, Kaplan-Meier method will be used to estimate survival probability. The calculated survival probability at a given time *t* is an estimator of survival probability beyond *t*, conditional on survival prior to the time *t*. The 2-sided point-wise 95% confidence limit will be calculated using the log-log transformation.

Mortality will be calculated. The causes of death and relatedness of death to surgical or medical procedure and/or the product(s) will be summarized in a table. All deaths will be listed.

Device deficiencies (DD) will be summarized by MedDRA terms and product type. All the device deficiencies will be listed.

Product related adverse events will be summarized by MedDRA terms and product type. The number of events and the number and percentage of subjects who experienced the event will be reported.

7.10 Safety Evaluation

Safety evaluation, such as the surgical or medical procedure related events, product related events, and device deficiencies will be summarized and listed as appropriate. Patient death will also be summarized and listed. Refer to 7.9 Evaluation of Objectives for details.

7.11 Changes to Planned Analysis

Any deviation from the analyses described in the statistical analysis plan and a justification for making the change will be documented in the final report if applicable or relevant study summary.

8. Validation Requirements

To ensure the quality of the statistical results and datasets created for the study, the following validation requirements will be implemented. Programs that contribute directly or indirectly to results pertaining to the primary objective including ADaM datasets and TLGs (Tables, Listings, and Graphs) development will be validated at level I or level II by a statistician or a statistical programmer. For the secondary objective, at least level II validation will be applied. Level III validation may be used for any previously validated program where only minor/administrative changes were made (e.g., change the location of the data directory). Any results that are used for external publication and reports should be validated at level I or Level II.

9. References

1. Rosner, Bernard, Fundamentals of Biostatistics, 4th edition, Duxbury Press