Medtronic **Statistical Analysis Plan v2.0 [Final]**	
Clinical Investigation Plan Title	**Poetry Study - PrOGrip™ Self-gripping Polyester Mesh Embedded REgisTRY for Abdominal Wall Sutureline Reinforcement in Subjects Undergoing Midline Laparotomy to Prevent Incisional Hernia**
Clinical Investigation Plan Identifier	MDT17048POETRY
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Confidentiality Statement [redacted]	

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1. Version History

Version	Summary of Changes	Author(s)/Title
v1.0 - 05Aug2019	• N/A (initial release)	[redacted] Sr Biostatistician, Corporate Biostatistics Medtronic
V2.0 – 05Nov2021	• Update of CIP version page 1 (V4.0) • Add Pregnancy Test (Section 5 page 7) • Demographic, risk factors and per-operative characteristics: measured on PAS, PPAS, SAS removed from Secondary Endpoints (alignment with CIP V4.0). • Update of Section 7.10 Safety evaluation is covered by secondary endpoints. Listing of AEs, SAEs, ADEs and SADEs, and U(S)ADEs will be provided based on Safety Analysis Set. AEs, SAEs, ADEs and SADEs, and U(S)ADEs will be analyzed using Medical Dictionary for Regulatory Activities (MedDRA v23.1) classification per System Organ Class and Preferred Term and they will also be assessed using the potential risks identified in the Clinical Investigation Plan. An Adverse Device Effect is an Adverse Event related to device and/or procedure.	[redacted] Sr Biostatistician, Surgical Innovations Medtronic

2. List of Abbreviations and Definitions of Terms

Term/Abbreviation	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.

Term/Abbreviation	Definition
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.
CI	Confidence Interval
CIP	Clinical Investigation Plan (can be used synonymously with Protocol)
Hernia	A clinically manifested bulge or a protrusion exacerbated by a Valsalva maneuver.
PAS	Performance Analysis Set
PMCF	Post Market Clinical Follow up
PPAS	Per Protocol Analysis Set – An analysis set a subset of the Performance analysis set, excluding subjects with major protocol deviation(s) and violation(s).
QOL	Quality of Life
SAE	Serious Adverse Event - Adverse event that: a) Led to a death, b) Led to a serious deterioration in the health of the subject, that either resulted in: 1) Resulted in a life-threatening illness or injury, or 2) Resulted in a permanent impairment of a body structure or a body function, or 3) In-patient or prolonged hospitalization, or 4) Medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or Led to fetal distress, fetal death or a congenital abnormality or birth defect. Note: Planned hospitalization for a pre-existing condition, or a procedure

Term/Abbreviation	Definition
	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.
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set – An analysis set including any subjects enrolled in the study.
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.
VAS	Visual Analog Scale is a psychometric response scale (0-10) which can be used in questionnaires to determine how much pain a subject is feeling.

3. Introduction

Although laparoscopic minimally invasive surgeries have increased in frequency, midline laparotomies are still common in both elective and emergency cases. After midline laparotomy, the prevalence of incisional hernias ranges between 10% and 54% depending on if the procedure was elective or emergency. (1-3) The presence of an incisional hernia can lead to complications such as bowel obstruction, incarceration, strangulation, and/or patient discomfort and pain. (4) Repair of incisional hernias requires additional procedure adding additional risk to the patient and finical costs. As a result, prevention of incisional hernias has become a common goal and in recent years, multiple studies have shown decreased frequency of incisional hernias when using prophylactic polypropylene mesh after midline laparotomies.

To that end, based on the expansive vast long-term data attained during the development of multiple surgical meshes for use in a variety of soft tissue repairs, Medtronic has developed the ProGrip™ self-gripping polyester mesh. Composed of knitted monofilament polyester with polylactic acid monofilament resorbable pins ProGrip™ self-gripping polyester mesh is intended for use in reinforcement of soft tissue where weakness exists, in procedures involving the repair of inguinal and incisional hernias or abdominal suture line reinforcement.

Medtronic has conducted a biocompatibility evaluation of ProGrip™ self-gripping polyester mesh, compliant with the standard EN ISO 10993-1 (2009), which demonstrates the biological safety of the device. Pre-clinical animal testing of ProGrip™ self-gripping polyester mesh demonstrates that the mesh shows the same inflammatory reaction as Parietex™ mesh (#0607CR023), similar gripping power to ProGrip™ self-gripping polypropylene mesh (#0607CR027) and contributes to the fixation of the mesh to the surrounding tissues better than Parietex™ mesh (#MC2009-004CR020). ProGrip™ Self Gripping Polyester has been available for use in inguinal and incisional hernia repair since 2008 and the available clinical data support a positive risk/benefit ratio.

The purpose of this study is to confirm the efficacy and safety of ProGrip™ Self-gripping Polyester Mesh for suture line reinforcement to reduce the incisional hernia incidence within 24 months in a minimum of 135 enrolled subjects undergoing procedures with midline laparotomies.

4. Study Objectives

4.1. Primary Objective

The primary objective of this investigation is to confirm the efficacy of ProGrip™ Self-gripping Polyester Mesh to reduce the incidence of incisional hernia within 24 months post-operatively in subjects undergoing procedure with midline laparotomies.

4.2. Secondary Objective

The secondary objective of this investigation is to confirm the safety of ProGrip™ Self-gripping Polyester Mesh through the occurrence of adverse device effects or procedure related adverse events following the use of ProGrip™ Self- gripping Polyester Mesh in subjects undergoing procedures with midline laparotomies.

5. Investigation Plan

This study is a prospective, multicenter, PMCF embedded registry study evaluating the use of the ProGrip™ Self-gripping Polyester Mesh in subjects undergoing midline laparotomy in order to prevent incisional hernia using the embedded registry data of Club Hernie in France.

The Club Hernie is a non-profit organization created in 2009, currently including 40 French surgeon permanent members, with the aim to improve the healthcare treatments in parietal surgery by an assessment of surgical

practices, promoting research in abdominal wall surgery using an internet database open to surgeon members to monitor their own hernia practice and outcomes.

This study utilizes the Club Hernie established registry database. This online database consists of systematic and consecutive data entry of all subjects treated for abdominal wall surgery with standard data captured of all preoperative, perioperative and post-operative data.

Subjects who meet the eligibility criteria will be considered for study participation and will be evaluated at screening/baseline, procedure, Day 1, discharge, Day 8, and 1, 12, and 24 months post-surgery. Enrollment period planned is 22 months in up to 12 sites in France. For this study Club Hernie permanent members, non-permanent and new members are considered for participation.

The duration of the study is estimated to be up to 46 months (22 months enrollment and 24 months follow-up). Screening for subject eligibility may occur up to 30 days (inclusive) prior to the procedure and post-procedure subjects will be assessed at Day 1, discharge, Day 8, and 1, 12, and 24 months. In total, subjects will participate in the study for a maximum of approximately 26 months, following the study schematic below:

Procedure/Assessment	Screening (Day -30 to 0)	Operative (Day 0)	Post-operative course (Day 0) Follow up	Post-operative course (Day 1) Follow up	Discharge Assessment	Post-operative course (Day 8, +/-2days) Follow Up	1 Month (Day 30, +/-1week) Follow-up	12 Months (-1/+4 weeks) Follow-up	24 Months (-1/+4 weeks) Follow-up
	Can be combined								
Eligibility criteria	X[1]	X[1]							
Informed consent	X[2]								
Pregnancy Test	X								
Subject demographics	X								
Relevant prior medical/surgical history	X								
Surgical Data									
Date of surgery		X							
Procedure indication		X							
Surgical technique for laparotomy closure		X							
Mesh reference and lot number		X							
Type of fixation		X							
Operative time		X							

Procedure/Assessment	Screening (Day -30 to 0)	Operative (Day 0)	Post-operative course (Day 0) Follow up	Post-operative course (Day 1) Follow up	Discharge Assessment	Post-operative course (Day 8, +/-2days) Follow Up	1 Month (Day 30, +/-1week) Follow-up	12 Months (-1/+4 weeks) Follow-up	24 Months (-1/+4 weeks) Follow-up
	Can be combined								
Mesh positioning and time		X							
Peri-operative events including adverse device effects or procedure related adverse events		X							
Surgeon satisfaction		X							
Post-operative data									
VAS pain assessment			X	X		X	X	X	X
Post-operative adverse events				X	X		X	X	X
Date of discharge					X				
Length of Hospital stay					X				
Physical exam including hernia clinical examination							X	X	X
Abdominal CT Scan								X	X
Quality of Life Questionnaire							X	X	X
Patient Satisfaction								X	X
1-month prior phone call including self-assessments								X	X
Study Exit									X

1. If Screening and Surgery occur on different days, these procedures should occur during Screening and be reconfirmed on the day of surgery.
2. 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.

6. Determination of Sample Size

Sample size is determined based on primary performance endpoint, assuming the superiority of ProGrip™ Self-gripping Polyester Mesh use to prevent incisional hernia vs no prevention of incisional hernia within 2-years following a midline laparotomy procedure.
The literature review showed an incisional hernia rate after midline laparotomies around 20% (9-16). Using a power (1-β) of 80% and a 5% error type I (two-sided), and considering a hypothetic incisional hernia rate of 10% for subjects with ProGrip™ Self-gripping Polyester Mesh, vs a theoretical hypothetic incisional hernia rate of 20% for subjects without any prevention following a midline laparotomy procedure, N= 108 evaluable subjects are required.
Assuming an attrition rate of 20% at 2-years, N=135 subjects will need to be enrolled.

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

Summaries of consented/screened, screen-failures and enrolled subjects will be provided overall. Screen failures reason(s) will be reported.
Subjects in the Safety Analysis Set (SAS), in the Performance Analysis Set (PAS) and in the Per Protocol Analysis Set (PPAS) will be summarized, according to follow-up.

Reason for study discontinuation will be tabulated based on Safety Analysis Set, Performance Analysis Set and Per Protocol Analysis Set.

7.1.2. Clinical Investigation Plan (CIP) Deviations

Subjects with protocol deviations will be summarized; protocol deviations (minor/major) and violations will be reported by type on both Safety Analysis and Performance Analysis Sets.

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

Statistical analysis will be performed on:

- Performance Analysis Set (PAS): includes all enrolled subjects excluding subjects who became pregnant during the follow-up, or subjects who undergo unscheduled abdominal surgery during study follow-up, which may increase the risk and cause of incisional hernia occurrence*.

*Subject follow-up data, starting from the event's occurrence, will be excluded/remove from the performance analysis.

- Per Protocol Analysis Set (PPAS): a subset of PAS excluding subjects with protocol violation and major protocol deviation(s) that may impact the primary endpoint assessment. More precisely, reason for exclusion may include but is not limited to:
  - Patient wrongly included (*i.e.* patient was enrolled but does not meet all the eligibility criteria).
  - Failure to obtain informed consent.
  - Deviation resulting from device use outside the recommended use in the IFU.
  - Patient who receives the incorrect device or device is misused

- Safety Analysis Set: includes all enrolled subjects.

Performance analyses will be run on Performance Analysis Set (PAS) and on Per Protocol Analysis Set (PPAS) as confirmatory analysis.

Safety analyses will be run on Safety Analysis set (SAS) and on Per Protocol Analysis Set (PPAS), as confirmatory analysis.

7.2. General Methodology

At the exception of Primary endpoint analysis which will be comparative (see details in section 7.9 Evaluation of Objectives), statistical analysis will be mainly descriptive.

Some subgroup comparative analyses may be run in addition to primary and secondary endpoints, to assess impact of demographic characteristics, risk-factors, indication for surgery, operative data and surgical technique applied.

- Qualitative variables will be described by their absolute and relative (%) frequencies of each class or value, and by two-tailed 95% confidence intervals.

- Quantitative variables will be described by their mean, standard deviation (SD), extreme values (minimum and maximum values), and number of missing data and by two-tailed 95% confidence intervals.

Continuous variables will be summarized using counts, means, and standard deviations, medians, minimum, maximum and 95% confidence Interval (CI).

Categorical variables will be summarized using absolute and relative (%) frequencies of each class or value, and by two-tailed 95% confidence intervals.

Statistical analysis will be implemented on overall subjects, using l analysis sets, as described previously (Section 7.1.3).

Comparative subgroup analyses will be performed using:
- 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 or t-test are not verified for continuous data.

Primary and secondary endpoints analyses are described in detail in section *7.9 Evaluation of objectives.*

Statistical analyses will be run using SAS® v9.4 system, and statistical outputs will be provided in text files.

7.3. Center Pooling

The study will be conducted in a minimum of 6 and maximum of 10 investigational sites. Baseline and surgical data will be summarized for overall subjects and for each site separately, to confirm homogeneity of subject's characteristics between sites.

Enrollment will not exceed 25 subjects per site, which avoid imbalance between sites.

Primary and secondary endpoint analysis will be run on overall subjects and sites.

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

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

7.5. Adjustments for Multiple Comparisons

Only one statistical analysis will be run for primary endpoint assessment (single testing), after all subjects completed the study. Therefore, there is no need for adjustment in the study.

7.6. Demographic and Other Baseline Characteristics

Demographics characteristics, medical/surgical histories and other risk-factors for incisional hernia occurrence will be summarized using descriptive statistics, based on Performance Analysis Set, Safety AS and per protocol AS.

7.7. Treatment Characteristics

Indication for abdominal surgery, operative data (such as ASA class, anesthesia and surgery duration), surgical technique for abdominal wall surgery as well as implanted mesh characteristics will be described. Some subgroup analyses may be run according to indication for surgery and surgical data, for efficacy and safety evaluation.

7.8. Interim Analyses

After half of the subjects completed the 1-year follow-up timepoint, an interim analysis (secondary endpoints assessment only) will be conducted for regulatory purpose.

7.9. Evaluation of Objectives

Primary Objective and Endpoint

The primary objective of this investigation is to confirm the efficacy of ProGrip™ Self-gripping Polyester Mesh to reduce the incidence of incisional hernia within 24 months post-operatively in subjects undergoing procedure with midline laparotomies.

The primary endpoint is the incisional hernia rate within 24 months of midline laparotomy assessed by CT-scan and physical examination including hernia clinical examination.
Statistical analysis of primary endpoint will be comparative. Binomial one-way test will be used to compare the observed ProGrip™ Self- gripping Polyester Mesh incisional hernia incidence rate to the 20% theoretical incidence rate (from no prevention population), using a two- sided alpha-level of 5%.

Primary endpoint will be measured using Performance Analysis Set; a confirmatory analysis of primary endpoint will be run using Per Protocol Analysis Set.

Secondary objective and endpoints

The secondary objective of this investigation is to confirm the safety of ProGrip™ Self-gripping Polyester Mesh through the occurrence of adverse device effects or procedure related adverse events following the use of ProGrip™ Self- gripping Polyester Mesh in subjects undergoing procedures with midline laparotomies.

To confirm the safety of ProGrip™ Self-gripping Polyester Mesh through the occurrence of adverse device effects or procedure related adverse events following the use of ProGrip™ Self- gripping Polyester Mesh in subjects undergoing procedures with midline laparotomies.
The following secondary endpoints will be assessed:

- Adverse event (AE) incidence reported by number, severity, seriousness and relationship to the procedure and device from the surgery to the 24-month visit: AE incidence will be measured on Safety Analysis Set.
- Time to incisional hernia occurrence: will be measured using Kaplan Meier estimates, and based on SAS, and PPAS.
- Post-operative pain at the site of surgery: will be measured on SAS and PPAS, at each postoperative timepoint: Day0 (after surgery), Day1, Day8, Day30, Month12 and Month24.
- Quality of life: will be measured on all, PAS, SAS, and PPAS, using Club Hernie QOL questionnaire, combining qualitative and quantitative data, at Month1, Month12 and Month24.
- Patient satisfaction: at 12 then 24 months, measured on PAS, PPAS and SAS
- Surgeon satisfaction, measured on PAS, SAS, and PPAS

7.10.Safety Evaluation

Safety evaluation is covered by secondary endpoints.
Listing of AEs, SAEs, ADEs and SADEs, and U(S)ADEs will be provided based on Safety Analysis Set. AEs, SAEs, ADEs and SADEs, and U(S)ADEs will be analyzed using Medical Dictionary for Regulatory Activities (MedDRA v23.1) classification per System Organ Class and Preferred Term and they will also be assessed using the potential risks identified in the Clinical Investigation Plan.
An Adverse Device Effect is an Adverse Event related to device and/or procedure.

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 endpoint analysis only.

Validation level III will be applied for any other study endpoint.

Validation levels are defined as follows:

- Level I: The peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer.
- Level II: The peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output.
- Level III: Original Statistical Programmer performs a visual inspection of the code and output to confirm functionality.

9. References

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10. Statistical Appendices

N/A