| Medtronic<br>**Statistical Analysis Plan v3.0 [Final]** | |
|---|---|
| **Clinical Investigation Plan Title** | A multi-center post-market single arm prospective study of Parietene™ DS Composite Mesh in subjects undergoing ventral hernia repair. |
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# Table of Contents

# 1. Version History

| Version | Summary of Changes | Author(s)/Title |
|---|---|---|
| [Final v1.0] | • N/A (initial release) | Mathilde Lourd,<br>Sr Biostatistician,<br>Corporate Biostatistics |
| [Final v2.0] | • Sections 7.2 and 7.9 Subgroup analyses performed | Sylvain ANSELME,<br>Sr Biostatistician,<br>Clinical Research and Medical Science. Surgical Innovations |
| [Final v3.0] | • **Page 1:** Update of CIP version: V4.0 (2021 12 03)<br>• **Section 5 page 8:** Add of "Remote or phone follow-up, medical record review, or follow-up with other healthcare practitioner may be utilized for 1-month, 3-month, 12-month and 24-month visits due to COVID-19 related reasons as explained in the CIP v4.0 and the Addendum VA."<br>• **Section 7.9 pages 14/15:**<br>- Removal of "and procedure related adverse events"<br>- Add of "Time to Device-related AEs occurrence may also be assessed using Kaplan Meyer estimates."<br>- Add of "Hernia recurrence will be assessed during physical examination at 1-month, 3-month, 12-month and 24-month assessment post-surgery. Remote follow-up visits due to COVID-19 related reasons may be performed: if hernia or hernia reoccurrence is suspected during a remote visit using questionnaires, the subject will be instructed to return to the clinic or hospital for diagnosis by the surgeon through clinical assessment. This process is fully accepted by scientific societies[5,6,7,8,9]".<br>• **Section 9 pages 17/18:** Move of all the references in this section (instead of footnotes) and add of new references related to remote visits. | Sylvain ANSELME,<br>Sr Biostatistician, Global Clinical Data Solutions |

# 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.<br>NOTE 1: 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.<br>NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device |
| 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.<br>NOTE 1: This definition includes events related to the investigational medical device or the comparator.<br>NOTE 2: This definition includes events related to the procedures involved.<br>NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. |
| ASA | American Society of Anesthesiologists |
| CCS | Carolina Comfort Scale: it is a validated, disease-specific, quality of life (QOL) questionnaire developed for patients undergoing hernia repair. |
| CE Mark | European Community Marking that indicates that the product (device) complies with the European Legislation and so can go to EU market. |
| CI | Confidence Interval |
| CIP | Clinical Investigation Plan (can be used synonymously with Protocol) |
| Device Deficiency | Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.<br>Note: Device deficiencies include malfunctions, use errors, and inadequate labeling. |
| FAS | Full Analysis Set – An analysis set including any subjects enrolled and receiving study device |
| Hernia recurrence | A clinically manifested bulge or a protrusion exacerbated by a Valsalva maneuver. |
| IA | Interim Analysis |
| IRB | Institutional Review Board |
| ISO | International Organization for Standardization |

| Term/Abbreviation | Definition |
|---|---|
| PMCF | Post market clinical follow up |
| PPAS | Per Protocol Analysis Set – An analysis set consisting of a subset of the full analysis set of subjects who meet the primary endpoint (12-month assessment) and who did not deviate (major) from the protocol |
| QOL | Quality of Life |
| SAE | Serious Adverse Event - Adverse event that:<br>a. Led to a death,<br>b. Led to a serious deterioration in the health of the subject, that either resulted in:<br>1. Resulted in a life-threatening illness or injury, or<br>2. Resulted in a permanent impairment of a body structure or a body function, or<br>3. In-patient or prolonged hospitalization, or<br>4. Medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or<br>c. Led to fetal distress, fetal death or a congenital abnormality or birth defect.<br>Note: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. |
| SADE | Serious Adverse Device Effect - Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. |
| SAP | Statistical Analysis Plan |
| SAS | Safety Analysis Set is an analysis set including any subject pre-operatively eligible for the study and with skin incision, including those who are 'screen failure during surgery. |
| USA | United States of America |
| UADE | Unanticipated Adverse Device Effect - Any serious adverse effect on health or safety or any life threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the CIP or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects. |
| 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.<br>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. |

| Term/Abbreviation | Definition |
|---|---|
| Ventral Hernia | A ventral hernia is a hernia of the abdominal wall excluding the inguinal area, the pelvic area and the diaphragm. |

# 3. Introduction

A ventral hernia is a hernia of the abdominal wall excluding the inguinal area, pelvic area, and the diaphragm. It is comprised of an abnormal protrusion of abdominal cavity contents or pre-peritoneal fat through a defect or weakness in the abdominal wall. Hernias may occur spontaneously (primary hernia) or at the site of a previous surgical incision (incisional hernia).

Hernias can only be repaired by surgical procedure. Operative repair of abdominal wall hernias forms a part of the daily routine practiced by every general and visceral surgeon. Approximately 4 million laparotomies are performed in the United States annually, up to 30%- 45% of them resulting in incisional hernia. Approximately 250,000 ventral incisional hernia repairs are performed annually in the United States. The repair of ventral hernias can be performed through either an open or a laparoscopic technique by a simple interrupted suture repair or a mesh repair.

Use of prosthetic mesh repair is considered as standard of care for ventral hernia treatment.
Depending on the surgical technique, the mesh may be implanted either in an intraperitoneal position, or outside of the abdominal cavity, such as onlay or inlay techniques. Surgical meshes are medical devices used to provide additional support to weakened or damaged tissue. The majority of surgical mesh devices currently available for use are constructed from synthetic materials and/or animal tissue. The mode of action of the mesh primarily relies on the strength provided by the structural component of the implant, i.e. the textile/tissue structure. The surgical mesh is intended to be progressively colonized by the host tissue following the cascade of biological mechanisms inherent to the wound healing and soft tissue remodeling, so that the mesh will ensure a long-term reinforcement of soft tissues.

Currently, various surgical mesh designs exist to accommodate the variety of surgical techniques in soft tissue repair and reconstruction by open and laparoscopic surgeries. In particular, composite meshes such as Parietene™ DS Composite Mesh, are composed of a textile with a temporary adhesion barrier on one side to allow intraperitoneal mesh placement during abdominal wall surgery while minimizing tissue attachment to the mesh in case of direct contact with the viscera.

The development of Parietene™ DS Composite Mesh relies on the long-term knowledge acquired by Medtronic in the development of surgical mesh for a variety of soft tissue repair procedures and the processing of implantable absorbable polymers. Parietene™ DS Composite Mesh was specifically developed as a fully synthetic alternative to the composite meshes currently available.

Medtronic has conducted a biocompatibility evaluation of Parietene™ DS Composite Mesh, compliant with the standard EN ISO 10993-1 (2009), which demonstrates the biological safety of the device. Pre-clinical animal testing comparing of Parietene™ DS Composite Mesh and Proceed™ Surgical Mesh (Studies 197164, 197165 and 198929), its predicate device, demonstrate that Parietene™ DS Composite Mesh achieves at least equivalent performance in terms of tissue integration and minimizing tissue attachment in case of contact to the viscera.

Parietene™ DS Composite Mesh obtained 510 K clearance in US (June 2017).

The post-market study on Parietene™ DS Composite Mesh in the US will serve to confirm the Safety and Performance of the product in the short, mid and long term for the repair of primary and incisional ventral hernia and to support EU regulatory approval and post-market requirements through a prospective single-arm study on N=125 male or female adult subjects will be enrolled at a minimum of 4 USA sites who are undergoing elective ventral hernia repair.

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

# 4. Study Objectives

## 4.1. Primary Objective

The primary objective of this study is to assess hernia recurrence, within 12 months following the use of Parietene™ DS Composite Mesh in ventral hernia repair.

## 4.2. Secondary Objective

The secondary objective of this study is to assess clinical outcomes, within 24 months following the use of Parietene™ DS Composite Mesh in ventral hernia repair.

# 5. Investigation Plan

This study is a single arm, prospective, multi-center, observational, US post-market study to confirm the clinical safety and performance of Parietene™ DS Composite Mesh in ventral hernia repair.

After IRB approvals, subjects who have signed an informed consent form (and who meet the eligibility criteria) and have received Parietene™ DS composite mesh will be enrolled in the study. Subjects will undergo elective ventral hernia repair using Parietene™ DS Composite Mesh and be evaluated pre-operatively, at the procedure, at discharge, within 1 month, 3 months, 12 months and 24 months post-surgery. Remote or phone follow-up, medical record review, or follow-up with other healthcare practitioner may be utilized for 1-month, 3-month, 12-month and 24-month visits due to COVID-19 related reasons as explained in the CIP v4.0 and the Addendum VA.

An interim analysis based on 30 subjects with complete 3-month visits to assess the short-term safety of the device will be used to support EU regulatory approval. Study enrollment will continue during interim analysis. The study will continue as a post market clinical follow up (PMCF) with extended follow-up of subjects to assess the mid (12 months) and long (24 months) term safety and performance of the device. The study will include a minimum of 125 subjects who will be followed 24 months post-surgery at a minimum of 4 USA sites. Subject participation in the study will last a maximum of 26 months and overall, the study is estimated to proceed for up to 38 months.

Study procedures and assessment are described in the study schematic below:

| Procedure/Assessment | Screening (Day-30 to 0) | Operative (Day 0) | Discharge Assessment | 1 Month (±14 days) Follow-up (Visit) | 3 Month (±14 days) Follow-up (Visit) | 12 months (±30 days) Follow-up (Visit) | 24 months (±30 days) Follow-up (Visit) |
|---|---|---|---|---|---|---|---|
| | Can be combined | | | | | | |
| Eligibility criteria | X[1] | X[1] | | | | | |
| Informed consent | X[2] | | | | | | |
| Subject demographics | X | | | | | | |
| Pregnancy status | X[1] | X[1] | | | | | |
| Medical and abdominal surgical history and relevant risk factors | X | | | | | | |
| Carolina Comfort Scale™ (Appendix B) | X | | | X | | X | X |
| Hernia defect description | | X | | | | | |
| Recurrence history if applicable | | X | | | | | |
| Date of surgery, Operative time | | X | | | | | |
| Anesthesia / ASA grade | | X | | | | | |
| Intraoperative wound contamination class | | X | | | | | |
| Indication for ventral hernia surgery | | X | | | | | |

| Procedure/Assessment | Screening (Day-30 to 0) | Operative (Day 0) | Discharge Assessment | 1 Month (±14 days) Follow-up (Visit) | 3 Month (±14 days) Follow-up (Visit) | 12 months (±30 days) Follow-up (Visit) | 24 months (±30 days) Follow-up (Visit) |
|---|---|---|---|---|---|---|---|
| | Can be combined | | | | | | |
| Type of access, defect closure and Surgical technique approach | | X | | | | | |
| Mesh size, lot number, positioning and fixation | | X | | | | | |
| Antibiotic prophylaxis | | X | | | | | |
| Area of mesh overlap | | X | | | | | |
| Surgeon satisfaction questionnaire | | X | | | | | |
| Adverse events assessment | | X | X | X | X | X | X |
| Length of hospital stay | | | X | | | | |
| Hernia recurrence/reoperation | | | | X | X | 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 has been determined based on an acceptable level of accuracy for the estimated rate of hernia recurrence at 12 months (primary endpoint).

Previous studies[1,2] of the predicate device (Proceed™ Surgical mesh) with similar study indications, population, and design (prospective study with a long-term follow-up with more than 100 subjects), have reported the incidence of recurrence at 12 months to range from 3.5% to 5.2%.

95% confidence intervals obtained from incidence rates between 3.5% and 5.2% with N=100 subjects are shown below. Precision of the recurrence rates range from ± 3.6% to ± 4.4% as the recurrence rate increases.

| | Recurrence rate at 12-month (1 year) | | | |
|---|---|---|---|---|
| | **3.5%** | **4.0%** | **4.5%** | **5.2%** |
| N | 100 | 100 | 100 | 100 |
| 95% CI | [0.0 % - 7.1 %] | [0.2% - 6.7%] | [0.4% - 8.6%] | [0.8% - 9.6%] |
| accuracy (+/-) | 3.6% | 3.8% | 4.1% | 4.4% |

Anticipating an attrition rate of 20% at 12 months, 125 subjects will be enrolled for this study.

# 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 Safety Analysis Set (SAS), in the Full Analysis Set (FAS), and in Per protocol Analysis Set (PPAS) will be summarized, according to follow-up, and within each investigational site.

Reason for study discontinuation will be tabulated based on FAS and SAS.

### 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

Statistical analysis will be performed on:

- Full Analysis Set (FAS): including any subject enrolled and receiving study device, representing the primary analysis population, for Efficacy and Safety analyses
- Per Protocol Analysis Set (PPAS): a subset of the FAS of subjects who meet the primary endpoint (12-month assessment) and who did not deviate (major) from the protocol, as confirmatory analysis for Efficacy and Safety analyses,
- Safety Analysis Set (SAS): any subject pre-operatively eligible with skin incision including those who are 'screen failure during surgery', used for Safety analysis.

## 7.2. General Methodology

Statistical analysis is descriptive; some subgroup comparative analyses may be run in addition to primary and secondary endpoints, to assess impact of demographic characteristics, risk-factors, hernia characteristics and/or surgical technique applied (including mesh characteristics).

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 frequencies, percentages and 95% confidence interval (CI).
Statistical analysis will be implemented on overall subjects, using several analysis sets, as described previously (Section 7.1.3).
Several comparative analyses will be performed by hernia type (primary hernia versus incisional hernia) on overall subjects and on a subgroup of subjects with robotically assisted laparoscopic repair. Results of subjects operated with robotically assisted laparoscopic repair will also be compared with subjects operated with a traditional laparoscopic procedure. The following statistical tests will be used:

- 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.

## 7.3. Center Pooling

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

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

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

No data imputation will be performed for missing data, excepted for (Quality of Life) Carolina Comfort Scale (CCS) Questionnaire analysis (see appendix A).

Subject's selection, practical monitoring all along the study will allow the most complete and accurate data collection.

For CCS questionnaires missing data, we apply the rules and programming code as described in the CCS User Guide (see Appendix B).

## 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/surgical histories and risk-factors will be summarized using descriptive statistics.

## 7.7. Treatment Characteristics

For efficacy and safety endpoints assessment, some subgroup analyses may be run according to hernia characteristics, surgical technique and mesh characteristic (number of treated hernias, mesh size, number of implanted meshes…) ; all these characteristics may impact efficacy and safety results.

## 7.8. Interim Analyses

2 interim analyses will be run according to the following milestones:

### 7.8.1. First interim Analysis

Preliminary analysis will be conducted in the study when 30 enrolled subjects complete the 3 month follow-up time-point. The objective is to confirm safety of the product at 3 months. This 3-month time-point is consistent with the wound healing period and the Parietene™ DS Composite Mesh film degradation profile (completely degraded by bulk hydrolysis in less than 15 weeks). This interim analysis is driven by regulatory needs, to support CE marking submission.

Through analysis of clinical data available on a predicate device (Proceed™ surgical mesh) and similar Medtronic composite meshes (Parietene™ Composite mesh, Parietex™ Composite mesh) used in ventral hernia repair (primary and incisional) by open or laparoscopic approach assessed during short-term post-surgery report the following adverse event rates:

10.6% on the equivalent, Proceed™ surgical mesh used in laparoscopic ventral hernia repair at 3-6 weeks follow-up[2],

14.3% on Parietene™ Composite mesh used in laparoscopic ventral hernia repair at 10 weeks follow-up (range 6-25 weeks)[3],

To 25%, on Parietex™ Composite mesh used in laparoscopic and open ventral hernia repair after 2 months follow-up with a population of 30 subjects[4].

Based on these studies, adverse event rates were estimated to range between 11% and 25% and used to generate binomial probabilities to observe at least 1 or 2 AEs with a sample size of 30 subjects as shown in the table below.

| **N=30 subjects** | **Hypothetic procedure related adverse event rate** | | | | | |
|---|---|---|---|---|---|---|
| prob. to observe: | 11% | 12% | 14% | 17% | 20% | 25% |
| **≥ 1** AE | 97.0% | 97.8% | 98.9% | 99.6% | 99.9% | 100.0% |
| **≥ 2** AEs | 85.7% | 89.0% | 93.6% | 97.3% | 98.9% | 99.8% |

With an N=30 of enrolled and evaluable subjects at the time of interim analysis, and assuming an 11% adverse event rate, there is a 97% probability to observe at least 1 adverse event and an 85.7% probability to observe at least 2 adverse events. In addition, the probability to observe adverse events increases as the adverse event rate increases to a maximum of 100% and 99.8% for observation 1 and 2 adverse events respectively at an adverse event rate of 25%.

First interim analysis (Safety analysis at 3-months) will evaluate subject's disposition, screening data, demographics and occurrence of procedure or device-related AE occurring within 3-month from surgery, including:

- ➔ Incidence of procedure and/or device-related AE occurring within 3 month from-surgery overall, and according to:
  - Relation to the procedure
  - Relation to the device including anticipated and unanticipated ADEs,
  - Severity,
  - Seriousness
  - Time of AE occurrence (intra-operatively, between surgery and discharge, and within 1 and 3 months post-surgery)

- ➔ Incidence of procedure and/or device-related AE occurring within 3 month from-surgery by SOC and PT
- ➔ Incidence of procedure and/or device-related SAE occurring within 3 month from-surgery by SOC and PT
- ➔ Listing of procedure and/or device-related AE
- ➔ Listing or procedure and/or device-related SAE

### 7.8.2. Second Interim Analysis

A second interim analysis is planned to occur when all enrolled subjects complete the 12-month visit, to assess both primary and secondary endpoints, when possible.

## 7.9. Evaluation of Objectives

Study objectives will be assessed through study endpoints measurement.

The primary endpoint is incidence of hernia recurrence within 12 months following Parietene™ DS Composite Mesh use in ventral hernia repair.

Incidence of hernia recurrence within 12 months will be measured on the FAS subjects and using the following calculation formula:

[Subjects with Recurrence diagnosed within the first 12month following surgery]

**/**

[Subjects with Recurrence diagnosed within the first 12month following surgery + Subjects free of recurrence with a follow-up ≥12months]

A confirmatory analysis of primary endpoint will be run using Per Protocol Analysis Set.

Secondary endpoints

- Incidence of adverse device effects (ADEs) intra-operatively, at discharge, within 1 month, 3 months, 12 months, and 24 months following Parietene™ DS Composite mesh use in ventral hernia repair will be primarily assessed based on FAS, and secondarily using PPAS and SAS.

- Incidence of hernia recurrence at 1, 3 and 24 months. The evaluation of hernia recurrence will be performed during a physical examination, using the formula described previously, according to the different time-points, and based on FAS and PPAS.

- Time to hernia recurrence and time to adverse device effect occurrence (from surgery time-point), will be assessed using Kaplan Meyer estimates. FAS and PPAS will be used for time to hernia recurrence, while FAS, PPAS and SAS will be used for time to ADE occurrence analysis. Time to Device-related AEs occurrence may also be assessed using Kaplan Meyer estimates.

- Carolinas Comfort Scale™ QOL questionnaires completed pre-operatively and at 1, 12 and 24 months postoperatively will be analyzed using the Carolina Comfort Scale User Guide recommendations and programming code (see Appendix B), and based on FAS and on PPAS.

Several Subgroup analyses will be performed. Comparative analyses will be performed by hernia type (primary hernia versus incisional hernia) on overall subjects and on a subgroup of subjects with robotically assisted laparoscopic repair. Results of subjects operated with robotically assisted laparoscopic repair will also be compared with subjects operated with a traditional Laparoscopic procedure.

Hernia recurrence will be assessed during physical examination at 1-month, 3-month, 12-month and 24-month assessment post-surgery. Remote follow-up visits due to COVID-19 related reasons may be performed: if hernia or hernia reoccurrence is suspected during a remote visit using questionnaires, the subject will be instructed to return to the clinic or hospital for diagnosis by the surgeon through clinical assessment. This process is fully accepted by scientific societies[5,6,7,8,9]

## 7.10.Safety Evaluation

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

- Relation to the procedure
- Relation to the device including anticipated and unanticipated ADEs,
- Severity,
- Seriousness.

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

## 7.11. Health Outcomes Analyses

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

## 7.12. Changes to Planned Analysis

Some minor changes were made in this SAP in regard to the statistical methodology as described in CIP v1.0 document. These changes are related to Analysis Sets definitions and the use of these analysis sets for endpoints assessment.

From CIP v1.0, analysis sets were defined as follows:

- the Full Analysis Set (FAS, including any subject enrolled and receiving study device) representing the primary analysis population,
- the Per Protocol Analysis Set [PPAS, a subset of the FAS of subjects who meet the primary endpoint (12-month assessment) and who did not deviate (major) from the protocol], as confirmatory analysis and,
- the Safety Analysis Set (any subject with skin incision including those who are 'screen failure during surgery') for safety and efficacy analysis

From SAP v1.0, analysis sets are defined as follows:

- Full Analysis Set (FAS): including any subject enrolled and receiving study device, representing the primary analysis population, for Efficacy and Safety analyses.
- Per Protocol Analysis Set (PPAS): a subset of the FAS of subjects who meet the primary endpoint (12-month assessment) and who did not deviate (major) from the protocol, as confirmatory analysis for Efficacy and Safety analyses,
- Safety Analysis Set (SAS): any subject pre-operatively eligible with skin incision including those who are 'screen failure during surgery', used for Safety analysis.

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

# 8. Validation Requirements

Validation level I will be applied for endpoints evaluated at the first interim analysis.

First interim analysis (Safety analysis at 3-months) will evaluate subject's disposition, screening data, demographics characteristics and occurrence of procedure or device-related AE occurring within 3-month from surgery (see IA#1 parameters in section 7.8.1.).

Validation level III will be applied for any endpoint evaluated during second interim analysis or final analysis.

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

1. Berrevoet F, Fierens K, De Gols J, Navez B, Van Bastelaere W, Meir E, et al. Multicentric observational cohort study evaluating a composite mesh with incorporated oxidized regenerated cellulose in laparoscopic ventral hernia repair. Hernia. 2009;13(1):23-7. doi: 10.1007/s10029-008-0418-5. PubMed PMID: 18682886.

2. Berrevoet F, Tollens T, Berwouts L, Bertrand C, Muysoms F, De Gols J, et al. A belgian multicenter prospective observational cohort study shows safe and efficient use of a composite mesh with incorporated oxidized regenerated cellulose in laparoscopic ventral hernia repair. Acta Chir Belg. 2014;114(4):233-8. PubMed PMID: 26021417.

3. Beldi G, Ipaktchi R, Wagner M, Gloor B, Candinas D. Laparoscopic ventral hernia repair is safe and cost effective. Surg Endosc. 2006;20(1):92-5. doi: 10.1007/s00464-005-0442-9. PubMed PMID: 16333538.

4. Balique JG, Benchetrit S, Bouillot JL, Flament JB, Gouillat C, Jarsaillon P, et al. Intraperitoneal treatment of incisional and umbilical hernias using an innovative composite mesh: four-year results of a prospective multicenter clinical trial. Hernia. 2005;9(1):68-74. doi: 10.1007/s10029-004-0300-z. PubMed PMID: 15578245.

5. Claessen JJM, Timmer AS, Atema JJ, Boermeester MA. Outcomes of mid-term and long-term degradable biosynthetic meshes in single-stage open complex abdominal wall reconstruction. Hernia. 2021 Dec;25(6):1647-1657. doi: 10.1007/s10029-021-02415-7. Epub 2021 Jun 7. PMID: 34097187.

6. Sneiders D, Jairam AP, de Smet GHJ, et al. Incisional hernia cannot be diagnosed by a patient-reported diagnostic questionnaire. J Surg Res. 2020;245:656–662. doi: 10.1016/j.jss.2019.07.030.

7. Williams AM, Bhatti UF, Alam HB, Nikolian VC. The role of telemedicine in postoperative care. mHealth 2018;4:11.

8. Vahagn C. Nikolian, Mudassir Akhter, Emaad J. Iqbal, Thomas Sutton, Ashraf Samhan, Sean B. Orenstein, Michael J. Rosen3, Benjamin K. Poulose. A National Evaluation of Surgeon Experiences in Telemedicine for the Care of Hernia and Abdominal Core Health Patients. World J Surg. 2022 Jan;46(1):76-83. doi: 10.1007/s00268-021-06332-9. Epub 2021 Oct 3.

9. Gunter RL, Chouinard S, Fernandes-Taylor S, Wiseman JT, Clarkson S, Bennett K, et al. Current use of telemedicine for post-discharge surgical care: a systematic review. J Am Coll Surg. 2016;222(5):915–927. doi: 10.1016/j.jamcollsurg.2016.01.062. - DOI - PMC - PubMed

# 10. Statistical Appendices

A. Quality of Life (QOL) Carolina Comfort Scale (CCS) Questionnaire

B. CCS QOL Questionnaire User Guide