STATISTICAL ANALYSIS PLAN

Title:	ATLAS (A prospective, multi-center Trial of a Long-term bio-Absorbable mesh with Sepra technology in challenging laparoscopic ventral or incisional hernia repair)
Protocol No.:	DVL-HE-017
Study Device:	Phasix™ ST Mesh
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1 Introduction

This document provides details of the statistical analysis plan (SAP) for the C.R. Bard, Inc. protocol DVL-HE-017. An interim analysis will be performed as soon as all subjects have reached 45 days follow-up or have withdrawn from the study earlier. The statistical methods described here are based on the analyses proposed in the Final Protocol issued on **March 23, 2016, Version 4.0.**

All data processing, summarization, and analyses will be performed using Statistical Analysis System (SAS), Version 9.4 software package.

2 Study Objective and Endpoints

2.1 Study Objective

The objective of this study is to collect additional data on safety, performance and effectiveness of Phasix™ ST in subjects receiving laparoscopic ventral or incisional hernia repair at high risk for SSO. Subjects at high risk are defined as having 1 or more of the following co-morbid conditions: body mass index (BMI) between 30-40 kg/m^2, inclusive, active smokers, chronic obstructive pulmonary disease (COPD), diabetes, immuno-suppression, coronary artery disease, chronic corticosteroid use, low pre-operative serum albumin, advanced age, or renal insufficiency. The study end points are described below.

2.2 Study Endpoints

2.2.1 Primary Endpoint

The Primary endpoint is Surgical Site Occurrence (defined as one of the following complications requiring intervention: surgical site infection, seroma, hematoma, wound dehiscence, skin necrosis, mesh infection and fistulas) within 45-days post-implantation.

2.2.2 Secondary Endpoints

1. Surgical Site Occurrence (SSO) (defined as one of the following complications requiring intervention: surgical site infection, seroma, hematoma, wound dehiscence, skin necrosis, mesh infection and fistulas) > 45-days post-implantation follow-up assessment
2. Hernia Recurrence Rate will be assessed by physical examination at each study visit through 24-months. A recurrent hernia will be defined as any hernia identified or confirmed by the investigator, during any study follow-up visit, within 5 cm of the hernia repaired in the study procedure.
3. Surgical Pain Scale - Visual Analog Scale (VAS)
4. Device-related adverse event incidence
5. Rate of reoperation due to the index hernia repair
6. Quality of life assessments (Carolinas Comfort Scale® and SF-12v2®)
7. Surgical procedure time as measured from incision to closure (skin to skin)

8. Length of stay in hospital (day of index surgery until day of discharge, LOS)

2.3 Overview

This is a prospective, multi-center, single-arm, open-label study designed to collect additional data on the safety, performance and effectiveness of Phasix™ ST for laparoscopic ventral or incisional hernia repair. Follow-up visits will be conducted at 1, 3, 6, 12, 18, and 24-months following surgery.

2.4 Sample Size Consideration

This study is projected to treat approximately 120 subjects at approximately 16 sites. The sample size of 120 subjects is based on potential adequacy of data to meet the study objectives. It is not based on any statistical consideration.

3 Population Sets

The Intent-to-treat (ITT) population consists of all enrolled subjects who have signed the Informed Consent Form. The modified ITT (mITT) population is defined as those subjects in the ITT population in whom Phasix™ ST Mesh has been implanted. A Per-Protocol (PP) population may be created if there are subjects who have any major protocol deviations. The PP population will consist of any subjects in the mITT population who do not have any major protocol deviations. The protocol deviations that are considered to have a "major" grade will be defined a priori.

All analyses will be primarily based on the mITT population. Analyses of the Primary endpoint may be performed for PP population as well.

4 Primary Endpoints

The primary endpoint is Surgical Site Occurrence (SSO) up to (and including) 45 days post implantation.

4.1 Definitions

The primary endpoint is defined as the rate of Surgical Site Occurrences (SSO) (requiring intervention) within 45 days post-implantation. SSOs are defined in this study as surgical site infection, seroma, hematoma, wound dehiscence, skin necrosis, mesh infection and fistulas.

4.2 Statistical Hypothesis

There is no formal statistical hypothesis for this post-market study. The study will follow high risk patients implanted with the Phasix™ ST for hernia repair for 24 months.

4.3 Primary Analysis

The proportions of subjects with SSO up to 45-days, and 95% confidence intervals of the rate from exact binomial test, will also be reported. Primary analysis is based on mITT population.

Reported start date of the SSO minus the date of the index hernia repair (implantation of the Phasix™ ST) will be used to determine if a SSO occurred within 45 days from index surgery. Any subjects discontinued before 45 days that do not have an SSO are considered as not evaluable and will be excluded from the analysis.

4.4 Sensitivity Analysis and Handling of Missing Data

The proportion of subjects with SSO up to 45-days along with 95% confidence interval will be estimated using the Kaplan-Meier method. Number of subjects with events, number of subjects censored and number of subjects left will also be presented.

The time to first event will be the time from index-procedure to the occurrence of the first event. Subjects who do not have a SSO before 45 days and do not discontinue the study before day 45 will be censored at day 45; subjects who discontinue before day 45 will be censored by their discontinuation day. If subjects discontinue at the surgery day then day 0.5 will be used as censor date. Note, the circumstances may be described separately.

A Kaplan-Meier graph will also be provided showing the survival curves for female and males separately.

Additionally, sensitivity analysis will be performed using PP population (if created).

5 Evaluation of Secondary Endpoints

5.1 Surgical Site Occurrence (SSO) > 45-days follow-up assessment

The proportion of subjects with SSO >45 days post-operatively (including all events post day 45 that are available at the time of the final report) and confidence intervals of the rate from exact binomial test will be reported.

If a subject discontinued within (≤) 45 days after index surgery, that subject is considered not evaluable and will be excluded from calculation of SSO rate after 45 days follow-up.

Analysis is based on mITT population.

5.2 Hernia Recurrence Rate

The proportion of subjects with Hernia Recurrence and confidence intervals of the rate from exact binomial test will be reported by each visit window, including both cumulative (overall rate) and disjointed intervals.

The start date of the hernia recurrence minus the implantation date will determine the interval of hernia recurrence.

Only evaluable subjects will be included in the denominator and evaluable subjects are defined as following: 1) For cumulative intervals, any subjects with Phasix™ ST Mesh implanted will be included in this analysis. 2) For disjointed intervals, if a subject discontinues before the intervals begins then that subject is considered as not evaluable for that particular interval analysis. Note: if subject did not come for a scheduled clinical visit (of the report period), but it was known that the subject was in the study and did not report hernia recurrence during the respective time interval, then the subject will be considered as free from the recurrence.

Hernia Recurrence in the same location as index procedure is identified by physical exam or any other means from post-operative CRF pages at scheduled or unscheduled visits. Analysis is based on mITT population (all subjects implanted with Phasix™ ST Mesh).

5.3 Surgical Pain Scale - Visual Analog Scale (VAS)

Subjects complete the pain VAS with 0 cm = "no pain" to 10 cm = "the worst pain imaginable" at baseline and at all post procedure visits.

The pain VAS length (cm) and its absolute change from baseline will be described with summary statistics by visit. Summary statistics by visit and absolute change from baseline will be presented with and without subjects taking pain medication within 24 hours of the pain VAS date. Analysis is based on mITT population.

5.4 Device Related Adverse Event Incidence

Adverse events that are possibly or definitely related to device will be included in the calculation of the device-related adverse event rate. In case of a missing classification of the relationship to device a relation to the device is assumed.

The proportion of subjects with device-related adverse event rate and confidence intervals of the rate from exact binomial test will be reported by each visit window, including both cumulative (overall rate) and disjointed intervals.

The start date of the device-related adverse event rate minus the implantation date will determine the interval of device-related adverse event.

A frequency table grouped by the Medical Dictionary for Regulatory Activities (MedDRA) dictionary of terms (system organ class (SOC) and preferred term (PT)) will be presented for number of subjects with device related AEs and total number of AEs.

Frequency tables for device related AEs by visit (presenting the number of subjects with events and total number of events) will be displayed.

Analysis is based on mITT population.

5.5 Rate of Reoperation due to Index Hernia Repair

The proportion of subjects with reoperation due to the index hernia repair and confidence intervals of the rate from exact binomial test will be reported by visit, including both cumulative and disjoint intervals.

Reoperation date will be compared to surgery date to determine the interval of reoperation.

Only evaluable subjects will be included in the denominator and evaluable subjects are defined as following: 1) For cumulative intervals, any subjects with Phasix™ ST Mesh implanted will be included in this analysis. 2) For disjoint intervals, if a subject discontinues before the intervals begins then that subject is considered as not evaluable for that particular interval analysis. Analysis is based on mITT population.

5.6 Quality of life assessments (Carolinas Comfort Scale® and SF-12v2™)

5.6.1 Carolinas Comfort Scale® (CCS)

The CCS is a 23-item questionnaire that measures sensation of mesh, severity of pain and movement limitations in the following eight domains: laying down, bending over, sitting up, performing activities of daily living, coughing or deep breathing, walking, walking up the stairs and exercising. The CCS is completed by the subjects at baseline and at all post

procedure visits. Each scale (sensation of mesh, pain or movement limitations) score (ranges from 0-5) is the average across the domains, and the total score (ranges from 0-5) is the average of the three scales scores.

CCS will be analyzed in accordance to the CCS user guide. Computational algorithms including the handling of missing values are described in detail in the guideline. In summary, the following rules will be applied:

1. Questions outcomes 0-5 will be used with lower scores indicating a more favorable health status.
2. Not applicable or no response will be handled as missing values.
3. Two or more outcomes ticked per question will be handled as missing value.

Absolute values and changes from baseline will be summarized with mean, standard deviation, minimum, median and maximum for each scale score and total score at each post baseline visit (except drain removal).

For each subject at each visit, if less or equal to two responses are missing within any of the three scales, the missing values will be replaced by the mean of the remaining responses of the scale at that visit. If more than two responses are missing within any scale for a visit, the whole survey at that visit will not be used for that subject.

Analysis is based on mITT population.

5.6.2 SF-12v2™

The 12-items in the SF-12v2™ are subset of those in the SF-36®. The SF-12v2™ includes one or two items from each of the eight health concepts. Thus, the SF-12v2™ measures eight concepts: Physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health.

The eight health concepts will be summarized in two components: Physical Components Summary, and Mental Component Summary. Data will be analyzed based on the guidelines of the SF-12v2™ instrument.

Analysis is based on mITT population.

5.7 Surgical Procedure Time as Measured from Incision to Closure (Skin to Skin)

The surgical procedure time (mins) of the index procedure is calculated as time of skin closure complete minus time of first incision.

Summary statistics will be presented for surgical procedure time. Analysis is based on mITT population.

5.8 Length of Stay in Hospital (Day of Index Surgery until Day of Discharge, LOS)

The LOS (days) at index procedure is calculated as date of hospital discharge (index procedure) minus date of hospital admission).

Analysis is based on mITT population.

5.9 Rate of mesh infection

The proportion of subjects with mesh infection and confidence intervals of the rate using exact binomial method will be reported cumulatively (overall rate) for each visit windows.

The start date of the infections minus the implantation date will determine the interval of infections.

5.10 Rate of surgical site infection

The proportion of subjects with surgical site infection and confidence intervals of the rate using exact binomial method will be reported cumulatively (overall rate) for each visit windows.

The start date of the infections minus the implantation date will determine the interval of infections.

6 Subgroup Analysis

By sex subgroup analysis will be performed for primary and Kaplan-Meier analysis (tables and curves) for primary and some secondary endpoints.

Where appropriate, further subgroup analysis (based on the mITT set) may be performed for the primary endpoint if enough subjects within the subgroups allow further insight to the data. Following subgroups are subject to further interest:

- Investigational Sites.
- Type of Procedure: Laparoscopic only versus Robotic Assisted.
- Surgical Technique: ‘Retro-rectus with CST’, ‘Retro-rectus without CST’, ‘Intra-Abdominal with CST’, ‘Intra-Abdominal without CST’ and ‘Other’.

7 Other Analysis

7.1 Subject Disposition

The summary of the number of subjects enrolled (ITT), implanted with Phasix™ ST Mesh (mITT), completed the study, and discontinued from the study by reason of discontinuation will be provided. Screen failures will be listed with inclusion/exclusion criteria that were not met. Summary may also be presented by site.

7.2 Protocol Deviation

The number of subjects with protocol deviations will be summarized by nature of the deviation. Protocol deviations will be summarized by site and period of occurrence. Additionally, protocol deviations will be listed with date of occurrence and the nature of deviation.

7.3 Demography and Background Disease Characteristics

Demographics and background disease characteristics will be summarized with descriptive statistics using the mITT analysis set. Summary statistics for categorical variables will include frequency counts and percentages and for continuous variables will include mean, standard deviation, minimum, median, and maximum.

Demographics and baseline characteristics variables include:

- Age at screening (year)
- Sex (Male, Female)
- Race (Asian, Black or African American, Caucasian and Other)
- Baseline Weight
- Baseline Height
- Baseline Body mass index (BMI) calculated from weight and height.

Background disease characteristics including medical history, wound classification, and hernia assessment will be summarized.

7.4 Pain Medication

All current pain medication is captured at baseline and all post implantation visit. Summary of the pain medication type (narcotic versus non-narcotic) will be provided.

7.5 Follow-up Period

The duration of follow-up period after the index surgery is calculated as:

Last day in study – date of the surgery

Last day in study is defined as latest of: discontinuation/completion day, last visit day or, last event (AE or reoperation during the study)occurrence day.

7.6 Surgical details

Summaries of the surgical details will be provided.

7.7 Surgical Drains

Surgical drain data will be summarized by the number of drains, number of subjects with surgical drains, corresponding surgery (index versus reoperation), placement, location and duration.

7.8 Device Failures

Device deficiencies will be summarized with number of deficiencies, number of subjects with device deficiencies, deficiency codes and reasons.

7.9 Adverse Events

AEs will be collected from the time of enrollment (AE onset after signing ICF) through the end of study participation (either study completion or screen failure or early discontinuation) and will be documented in the medical record or source document and on study eCRFs. All events will be followed to satisfactory resolution or stabilization. AEs that occur prior to the surgical procedure will be added to the medical history. AEs that occur from the time of

surgical procedure will be recorded in the source documentation and on the AE page of the eCRF

AEs will be tabulated by system organ class (SOC) and preferred term (PT) (MedDRA). The total number of events, as well as the number and percentage of subjects with events will be reported. Subjects will also be summarized by severity groups. SAEs will be summarized by SOC and PT.

Subjects with AEs related to the procedure (definitely or possibly related; in case of a missing classification of the relationship to procedure a relation to the procedure is assumed) will be summarized with frequency and percentage. Device related AEs will be summarized similarly.

Subjects who do not have Phasix™ ST implanted will have their AEs summarized separately and their outcome data will not be collected or analyzed.