CLINICAL STUDY PROTOCOL

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 Number:	**DVL-HE-017**
Study Type:	**Post-market, multi-center, prospective, single-arm, open label**
Date:	**April 16, 2018**
Version:	**5.0**
Study Devices:	**Phasix™ ST**
Sponsor:	**Davol Inc.** **Subsidiary of C.R. Bard, Inc.** **100 Crossings Boulevard** **Warwick, RI 02886** **Phone: 1-800-556-6756**
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Protocol Signature Page

The Investigator agrees to conduct the clinical study, which is the subject of this protocol, in accordance with the Clinical Study Agreement, this protocol, all applicable laws and regulations, and the conditions of approval imposed by the reviewing Institutional Review Board.

Agreed to by (Investigator):

_____
Printed Name – Investigator

_____
Signature – Investigator

_____
Date

Protocol Abbreviations/Acronyms

Abbreviation/Acronym	Definition
A1C	Glycated hemoglobin
AE	Adverse event
Bard	C. R. Bard, Inc.
BMI	Body Mass Index
°C	Degrees in Celsius
CBGB	Coronary Artery Bypass Graft Procedures
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
cm	Centimeter
CMC	Carboxymethylcellulose
COPD	Chronic Obstructive Pulmonary Disease
C-section	Cesarean Section
CST	Component Separation Technique
CT	Computed Tomography Scan
CV	Curriculum vitae
DIP	Deep Incisional Primary
DIS	Deep Incisional Secondary
doi	Digital object identifier
eCRF	Electronic Case Report Form
e.g.	For Example
ET	Early Termination
et al.	Et alia (and others)
etc.	Et cetera
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
g/dL	Grams per deciliter
HA	Hyaluronate
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
i.e.	That Is
IFU	Instructions For Use
Inc.	Incorporated
IRB	Institutional Review Board
ITT	Intent to Treat
kg/m^2	Kilograms per meter squared
LTFU	Lost to Follow-Up
mg/dL	Milligrams per deciliter
mITT	Modified Intent to Treat
ml	Milliliter
mm	Millimeter

MRI	Magnetic Resonance Imaging
OGTT	Oral Glucose Tolerance Test
OTC	Over-the-counter
P4HB	Poly-4-hydroxybutyrate
PDS	Polydioxanone
PEG	Polyethylene glycol
PGA	Polyglycolic acid
PP	Per-Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-12®	12-Item Short Form
SIP	Superficial Incisional Primary
SIS	Superficial Incisional Secondary
SSI	Surgical Site Infection
SSO	Surgical Site Occurrence
ST	Sepra® Technology
™	Trademark
US	United States
VAS	Visual Analogue Scale
WOCBP	Women of Childbearing Potential

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1 INTRODUCTION

1.1 Background

With more than 2 million abdominal operations occurring annually in the United States (US), up to 20% of those patients developing ventral incisional hernias, abdominal wall defects and incisional hernias represent a challenging surgical condition.[1, 2] Approximately 348,000 ventral hernia repairs are performed on a yearly basis.[3] There are several options for repair, including primary repair, synthetic or biologic material placement, repair with relaxing incisions, and use of musculofascial flaps, utilizing both open and laparoscopic approaches.[2] However, there is no clear-cut consensus regarding the optimal hernia repair technique, particularly in complex hernia repair cases where patient co-morbidities exist and a high risk of infection is present.

Simple suture repair has been associated with a high risk of hernia recurrence, with reports ranging from 10% to 55%, and has been nearly abandoned for the repair of hernias which are greater than five centimeters (cm) in size.[4, 5, 6, 7] Use of synthetic mesh reduces hernia recurrence rates, although its use has been associated with complications such as infection, adhesions, fistulae, and foreign body reactions including increased inflammation and/or connective tissue deposition.[8]

Synthetic mesh repair procedures, either open or laparoscopic, have been reported to lead to fewer recurrences compared to primary repairs.[9, 10, 11] Improved outcomes are believed to be related to reduced tension on the fascial edges and sutures when mesh is used in hernia repair procedures. However, complex cases and large abdominal wall defects continue to pose a challenge to surgeons. Factors such as patient co-morbidities, defect size, location, tissue viability and degree of contamination are included in a surgeon's assessment and decision-making process.[12] These large abdominal wall defects have been associated with recurrence rates of up to 46%.[13]

Laparoscopic ventral hernia repair was first reported by LeBlanc in 1992, and is popular alternative to open repairs due to the potential benefit of shorter hospital stays, improved patient outcomes, and fewer complications compared to open repairs.[14, 15] In a large series (850 patients) by Heniford, et al., laparoscopic ventral hernia repair using prosthetic mesh had a low rate of conversion to open surgery (3.4%), length of hospital stay (2.3 days), a moderate complication rate (13.2%), and a low hernia recurrence rate of 4.7% (average follow-up of 20 months).[15] In a study by Orenstein, et al., laparoscopic ventral hernia repair with defect closure had a low recurrence rate (none in 47 consecutive patients out to 16.2 months follow-up).[16] They purported that defect closure eliminated postoperative seromas and patient reports of bulging and reduced the size of implanted mesh.[16]

Ideally, a resorbable mesh would provide adequate structural support throughout the healing process and would be fully absorbed when the wound has completely healed, thereby potentially reducing the chances for complications associated with the persistence of non-resorbable mesh material. However, the development of resorbable mesh products has faced

challenges related to the rate of resorption with complications arising when the mesh product is resorbed too quickly. Rapid resorption does not support sufficient healing if structural reinforcement is diminished during the tissue repair period. A resorbable mesh should retain its functional strength for a sufficient period of time to allow native cellular ingrowth tissue remodeling, maturation of collagen, and gradual shift of mechanical load.

Phasix™ Mesh is a commercially available medical device in the US. It is a resorbable mesh prepared from poly-4-hydroxybutrate (P4HB) which has been studied for use as a biomaterial for a number of applications in medical devices and tissue engineering due to favorable mechanical properties, biocompatibility and desirable degradation times.[17,18,19] Using standard measures of mechanical strength (suture pull-out, tear and ball burst strength) Phasix™ Mesh is comparable in performance to traditional polypropylene mesh. Pre-clinical implantation studies indicate that the resorption of the Phasix™ Mesh fibers is minimal throughout the 12 week expected period of healing and up to ~26 weeks post-implantation. Resorption of the fibers is essentially complete in 12-18 months.[21, 22] Given the long-term strength retention observed in preclinical studies, it is anticipated that Phasix™ Mesh may result in low recurrence and complication rates with minimal pain and discomfort when used for hernia repair.

A porcine hernia repair study demonstrated that Phasix™ Mesh could perform as a durable scaffold for soft tissue repair.[21] The results of the 52-week study showed that the repair site had significantly greater mechanical repair strength, as compared to native abdominal wall. Notably, repair strength persisted even after significant Phasix™ Mesh resorption (as measured by molecular weight). Histologically, Phasix™ Mesh showed an initial mild-moderate host inflammatory response, that declined to mild over 52-weeks.

Neovascularization (angiogenesis) and new collagen deposition were evident at 6, 12, 26 and 52-weeks. In a 24-week rat study, histological analyses of the repair site demonstrated that other fully-resorbable competitive meshes had a greater overall host inflammatory response, whereas the response to Phasix™ Mesh was relative comparable to permanent polypropylene mesh.[22] In the same study, histological analyses demonstrated similar variability on measures of host fibrotic response.

The subject of this study, Phasix™ ST is a fully resorbable mesh with a hydrogel coating that is also resorbable. It is a sterile mesh device with indication for use in the reinforcement of soft tissue, where weakness exists, in procedures involving soft tissue repair, such as for the repair of hernias. Phasix™ ST Mesh is comprised of a co-knitted mesh and hydrogel coating.

The fascial side of the mesh allows for a prompt fibroblastic response through the interstices of the mesh, allowing for complete tissue ingrowth, similar to P4HB mesh alone. The visceral side of the mesh is coated with a resorbable, chemically modified sodium hyaluronate (HA), carboxymethylcellulose (CMC), and polyethylene glycol (PEG) based hydrogel. The resorbable hydrogel coating functions to separate the mesh from underlying tissues and organ surfaces to help minimize tissue attachment to the mesh. Shortly after hydration in saline, the biopolymer coating becomes a hydrated gel that is resorbed from the site in less than 30-days. See Section 1.3 Device Description, for more information.

A laparoscopic, porcine study was conducted to evaluate peritoneal tissue attachment development 4 weeks after implantation of Phasix™ ST Mesh or Ventralight ™ ST Mesh (each group used 4 pigs; 8 meshes). At 4 weeks post-implantation, there were very few instances of light, omental tissue attachments in both groups. The overall tissue attachment scores associated with Phasix™ ST Mesh was not significantly different than for Ventralight™ ST Mesh. These results indicate that the hydrogel barrier (Sepra® Technology) properties associated with Ventralight™ ST Mesh are maintained with Phasix™ ST Mesh.[22]

Additional porcine studies were conducted to characterize the strength of a buttress repair over time. Twenty-four, female, Yucatan pigs were implanted bilaterally with mesh according to one of the following: a) underlay repair with Phasix™ ST Mesh; b) underlay repair with Ventralight™ ST Mesh; c) a retromuscular repair with Phasix™ Mesh or d) a retromuscular repair with Strattice™ Firm Reconstructive Matrix. Bilateral surgical defects (1" diameter) were created and subsequently repaired with PDS suture. Mesh devices were placed and fixated with absorbable tacks or sutures. Ball burst strength and host responses were measured at mesh placement and 12- or 24-weeks post-implantation.[22]

At 12- or 24-weeks, the burst strength of the Phasix™ ST Mesh repair was at, or slightly above, the burst strength at the time of mesh placement (despite the hydrolysis of the Phasix™ material over these time periods). This suggests a transfer of load from the degrading Phasix™ material to the newly ingrown host tissue. The Strattice™ Firm Reconstructive Matrix repairs showed a significant reduction in strength of the repair site at 12- or 24-weeks and they had significantly lower burst strength relative to Phasix™ and Phasix™ ST Mesh devices. At 12- or 24-weeks, histology demonstrated that a robust and biocompatible ingrowth is associated with the Phasix™ material. Neovascularization occurs more rapidly in the Phasix™ material relative to the Strattice™ Firm Reconstructive Matrix.[22]

This post-approval clinical study is being conducted to evaluate the use of Phasix™ ST Mesh in laparoscopic ventral or incisional hernia repair in patients with a higher level of risk for Surgical Site Occurrence (SSO) as defined by the presence of 1 or more comorbid conditions. Patients who receive a Phasix™ ST implant will be followed for 24-months.

1.2 **Rationale**

This study is intended to evaluate the use of Phasix™ ST for laparoscopic ventral or incisional hernia repair amongst subjects at high risk for SSO.

1.3 **Device Descriptions**

1.3.1 Phasix™ ST

Phasix™ ST is a fully resorbable mesh with a hydrogel coating that is also resorbable. It is a sterile mesh device with indication for use in the reinforcement of soft tissue, where weakness exists, in procedures involving soft tissue repair, such as for the repair of hernias. Phasix™ ST Mesh is comprised of a co-knitted mesh and hydrogel coating.

Preclinical implantation studies indicate that resorption of the P4HB fibers is minimal throughout the 12 week expected healing period, and remains minimal up to 26-weeks post implantation. Significant degradation of the mesh fibers observed in preclinical studies within 12- to 18-months indicates loss in mechanical integrity and strength of the mesh. While fiber segments were observed at 18-months, they continued to degrade.[20, 21]

The fascial side of the mesh allows for a prompt fibroblastic response through the interstices of the mesh, allowing for complete tissue ingrowth, similar to P4HB mesh alone. The visceral side of the mesh is coated with a resorbable, chemically modified sodium hyaluronate (HA), carboxymethylcellulose (CMC), and polyethylene glycol (PEG) based hydrogel. The resorbable hydrogel coating functions to separate the mesh from underlying tissues and organ surfaces to help minimize tissue attachment to the mesh. Shortly after hydration in saline, the biopolymer coating becomes a hydrated gel that is resorbed from the site in less than 30-days.

Phasix™ ST Mesh and Phasix™ Mesh are similar in material; with both containing P4HB, the largest percentage of material present in Phasix™ ST Mesh. The difference between the meshes is that Phasix™ Mesh does not have polyglycolic acid (PGA) fibers or a hydrogel coating.

Phasix™ ST Mesh was designed to handle similarly to polypropylene (permanent) mesh at implantation, but it is fully resorbable. It is expected to maintain its strength over the critical healing period; minimize tissue attachment to the mesh, and resorbs, leaving no foreign material behind.

Phasix™ ST is commercially available in the US and indicated for use in the reinforcement of soft tissue, where weakness exists, in procedures involving soft tissue repair, such as for the repair of hernias. Because Phasix™ ST Mesh is fully resorbable, it should not be used in repairs where permanent wound or organ support from the mesh is required. A full description of Phasix™ ST is included in the product's Instructions for Use (IFU).

2 STUDY OBJECTIVES

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, immunosuppression, coronary artery disease, chronic corticosteroid use, low pre-operative

serum albumin, advanced age, or renal insufficiency. The study end points are described below.

3 STUDY ENDPOINTS

There is one primary endpoint, SSO, and eight secondary endpoints:

3.1 **Primary Endpoint**

1. Surgical Site Occurrence (defined as and of the following complications requiring intervention: surgical site infection (see Appendix 2 for definitions), seroma, hematoma, wound dehiscence, skin necrosis, mesh infection and fistulas) within 45-days post-implantation.

3.2 **Secondary Endpoints**

1. Surgical Site Occurrence (defined as surgical site infection (see Appendix 2 for definitions), seroma, hematoma, wound dehiscence, skin necrosis, mesh infection and fistulas requiring intervention) > 45-days post-implantation
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-12®)
7. Surgical procedure time as measured from incision to closure (skin to skin)
8. Length of stay

4 STUDY DESIGN

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. See Section 6 for a detailed schedule of study visits and procedures.

5 STUDY POPULATION

5.1 **Number of Subjects**

This study is projected to treat approximately 120 subjects at approximately 16 US sites.

5.2 **Eligibility Criteria**

5.2.1 Inclusion Criteria

The subject must meet all of the criteria listed below to be treated in the study:

1. Subject must be 18 years of age or older
2. Subject must be willing to give written informed consent
3. Subject must be diagnosed with ventral or abdominal incisional hernia
4. Subject must be willing to undergo laparoscopic hernia repair using intraabdominal placement (with or without Component Separation Technique (CST))
5. Surgeon must be able to fully close the hernia defect. Defect closure is defined as complete re-approximation of fascial edges, leaving no gap. Since the safety and effectiveness of Phasix™ ST Mesh in bridging repairs has not been evaluated or established, the defect should be closed prior to mesh use.
6. Subject is expected to meet the criteria for a Class I wound as defined by the CDC (Appendix 3)
7. Subjects must have 1 or more of the following pre-study conditions:
    a. Body Mass Index (BMI) between 30-40 kg/m^2, inclusive
    b. Active smoker (including if attempts to quit smoking within two weeks of surgery have failed and the patient is still an active smoker at the time of surgery)
    c. COPD presence on patient self-report
    d. Diabetes mellitus (if yes, diagnosis to be confirmed via medical records or laboratory results according to 2014 Joslin Clinical Guideline for Adults with Diabetes)(Appendix 5)
    e. Immunosuppression
    f. Coronary Artery Disease
    g. Chronic corticosteroid use: greater than 6 months systemic use
    h. Serum albumin less than 3.4 g/dL
    i. Advanced age: 75 years or older
    j. Renal insufficiency, defined as serum creatinine concentration ≥2.5 mg/dL

5.2.2 Exclusion Criteria

The subject must be excluded from treatment in the study if any of the following criteria are met:

1. Subject has had 4 or more previous hernia repairs (of the index hernia)
2. Subject's hernia is > 350 cm^2
3. Complete removal of existing mesh from a prior hernia repair (in the same affected area) is not possible
4. Subject has intact permanent mesh adjacent to the current hernia to be repaired
5. Preperitoneal placement of mesh
6. The subject is known to have a collagen disorder
7. The subject has peritonitis

8. The subject is on or suspected to be placed on chemotherapy medications during any part of the study
9. The subject's Body Mass Index (BMI) is > 40 kg/m^2
10. The subject has cirrhosis of the liver and/or ascites
11. Subject is American Society of Anesthesiology Class 4 or 5
12. Subject has a life expectancy of less than 2 years at the time of enrollment
13. Subject has any condition that, in the opinion of the Investigator, would preclude the use of the study device, or preclude the subject from completing the follow-up requirements
14. Subject has a surgical wound classified as Class II (Clean-Contaminated), Class III (Contaminated) or Class IV (Dirty-Contaminated) as defined by the CDC (Appendix 3)
15. Subject has an active or latent systemic infection
16. Patient has a contraindication to placement of mesh
17. Subject requires surgical bridge repair as the sole repair
18. Subject is pregnant or has plans to become pregnant during the study period
19. Subject has enrolled in another interventional clinical study within the last 30 days
20. Subject is part of the site personnel directly involved with this study
21. Subject has a known allergy to the test device or component materials (patients with known allergies to tetracycline hydrochloride or kanamycin sulfate should be avoided).

6 STUDY PROCEDURES

6.1 Subject Screening and Baseline Evaluation

Subjects with a diagnosis of ventral or abdominal incisional hernia receiving laparoscopic surgical repair (including robotic-assisted repairs) with defect closure, will be screened for potential eligibility against the study protocol inclusion and exclusion criteria, utilizing ordinary standard of care procedures (e.g., physical examination, blood work, medical evaluation) within 60 days of the date of consent. Since the safety and effectiveness of Phasix™ ST Mesh in bridging repairs has not been evaluated or established, the defect should be closed prior to mesh use. This may include a full anesthetic work-up customary for hernia repair procedures. Any other standard of care examination or evaluation within 60 days of the date of consent may be considered baseline for study purposes. Prior medical records documenting these tests, examinations and evaluations may be used as the source documents for the baseline visit.

During the screening and recruitment process, the Investigator will be responsible for describing the nature of the clinical study, verifying that the eligibility criteria have been met, and obtaining informed consent. Written informed consent and a Health Insurance Portability and Accountability Act (HIPAA) waiver must be obtained prior to performance of any protocol specific procedures.

The following screening/baseline procedures will be conducted and documented.

6.1.1 Informed Consent

The investigator will explain the study to the subject, answer all of the subject's questions, and obtain written informed consent in a language in which the subject is fluent before the collection of any study data or performance of any study procedures.

The subject must be willing and able to sign and date the informed consent form (ICF) prior to the collection of study data or performance of any study procedures. The original, signed informed consent will be retained with the subjects' records and a copy provided to the subject.

6.1.2 Enrollment

Subjects who sign an informed consent will be considered enrolled in this study. Subjects who provide consent for participation but do not meet all of the study eligibility criteria and do not receive the study device will be considered screen failures.

6.1.3 Eligibility

The subject's eligibility for study enrollment will be reviewed and documented on the appropriate eCRF. At the time of screening, a related progress note must be entered in the source documentation to indicate that all eligibility criteria were reviewed and screening results noted. Final eligibility will be determined intraoperatively.

Subjects who fail to meet eligibility criteria should be considered screen failures and treated according to the Investigator's standard of care. Data are to be collected for screen failure subjects from the time the ICF is signed until the subject is deemed a failure. At a minimum, subject demographics and the reason for failure must be collected. Adverse events (AEs) that occur prior to the surgical procedure will be added to the medical history. Any adverse event that occurs from the beginning of the surgical procedure until the subject is determined as screen failure will be recorded on the AE eCRF.

6.1.4 Evaluation of Pregnancy Status

The pregnancy status of potential study subjects will be evaluated as part of the screening assessment as follows:

Women of child bearing potential (WOCBP) must undergo a pregnancy test (urine or blood). A negative pregnancy test (urine or blood) must be obtained within 7 days of the surgical procedure.

Women who are postmenopausal or not of child bearing potential (e.g. status post hysterectomy or tubal ligation, no menses in the past 12 months): status must be recorded to note that the subject is not of child bearing potential.

6.1.5 Assignment of Subject Screening Number

Subject numbers will be assigned in sequential order, consisting of six digits where the first three digits designate the study site and the last three digits designate the subject number (i.e., subject number 101 001 will be the first subject at site 1; 101 002 will be the second subject at site 1, etc.).

6.1.6 Blinding

The study is an open-label study with a single treatment condition. Subjects, investigator (and surgeon) will not be blinded to the study treatment.

6.1.7 Demographics and Medical History

The subject's medical history and demographic information will be documented on the appropriate eCRF. Demographic information will include gender, date of birth, race and ethnicity.

6.1.8 Physical Examination

A standard physical exam, appropriate to subjects about to undergo abdominal surgery, will be performed by the physician. Height and weight measurements will be recorded to allow for the calculation of BMI. The subject's ability to participate and meet the follow-up requirements will be established.

6.1.9 Concomitant Pain Medication Usage

All pain medication taken within 24 hours of each study visit will be recorded in the source documentation at baseline and at each follow-up visit. A designation of narcotic and non-narcotic pain mediation will be recorded in the eCRF.

6.1.10 Patient Reported Outcome Assessments

Subjects will complete the Surgical Pain Scale -VAS, Carolinas Comfort Scale® and SF-12® to measure pain, discomfort and quality of life.

6.2 **Surgical Procedure**

6.2.1 General Procedures

All subjects will undergo laparoscopic ventral hernia repair. Subjects will be administered pre-operative antibiotics according to hospital protocol. There is an intraoperative exclusion for hernias >350 cm^2. All other intraoperative exclusion criterion should be verified (e.g., a

surgical wound classified as clean-contaminated, contaminated or dirty; absence of an active or latent systemic infection; presence of peritonitis; a hernia bridge as the sole repair procedure) as final eligibility is determined intraoperatively.

The surgical technique will require intraabdominal (using absorbable sutures or tacks) mesh placement (with or without CST). Ensure proper orientation (see IFU for details); the coated side of the prosthesis should be oriented against the bowel or sensitive organs. Do not place the uncoated mesh side against the bowel. There is a risk for adhesion formation or erosions when the uncoated mesh side is placed in direct contact with the bowel or viscera.

The Phasix™ ST Mesh can be tailored without fraying or unraveling and offers bi-directional elasticity to adapt to various stresses encountered in the body. Use a sharp surgical instrument (scissors) to trim the mesh. To minimize chance of recurrence, trim the mesh such that it is large enough to provide sufficient overlap beyond the margins of the defect. If the material is cut too small, tension may be placed on the suture line, which may result in a recurrence of the original defect. The mesh is to be positioned so its edges extend beyond the margins of the defect by at least 5 cm. It is recommended that fixation be placed at approximately every 1 to 2 cm intervals. The edges are then fixated to assure proper closure under correct tension.

If a prior hernia repair utilizing mesh is in the same area to be treated for the study, complete removal of existing mesh is required for the subject to remain eligible for the study. Subjects with intact permanent mesh adjacent to the study hernia to be repaired are excluded from the study. Once all of the dissection is performed and all of the hernia has been exposed, the largest vertical and transverse dimensions should be recorded.

The procedure may include CST to obtain site closure. All skin incisions will be closed with staples and/or sutures and wounds will be dressed with sterile occlusive dressings.

6.2.2 Postoperative Care

If for any reason the mesh is removed and a mesh infection is suspected, routine culture, at the site of the wound, area of contamination, or potential contamination, obtained according to the instructions in Appendix 4 to determine cell count and type (i.e., yeast, gram positive or gram negative bacteria, or other). If genus and species of the culture are identified as part of the routine practice at the site, that information should be recorded.

6.2.3 Surgical Details

Surgical details will be recorded and entered in the appropriate source documentation and eCRF(s). Details will include but may not be limited to procedure date, start/stop times, concomitant procedures, procedure related complications and AEs.

6.3 **Subject Follow-up**

6.3.1 Subjects Not Implanted and Surgical Repair Failures

Subjects who are screened but do not have the study device placed should be considered screen failures and treated per hospital standard of care. Screen failure subjects who experience a protocol defined AE will be followed through satisfactory resolution or stabilization of the event.

Reason for failure of the surgical repair procedure, as well as all information outlined in Section 6.2.2 must be recorded in the source documentation.

6.3.2 Subjects Successfully Implanted

Subjects successfully implanted with Phasix™ ST will be followed as per the protocol defined follow-up procedures (see Table of Study Events).

6.3.3 Assessments

Subjects should report to their respective study site for follow-up visits at the following postoperative times:

- Pregnancy test for WOCBP within 7 days of index surgery
- 1 month: Day 30 $\pm$ 7 days
- 3 month: Day 90 $\pm$ 30 days
- 6 month: Day 180 $\pm$ 30 days
- 12 month: Day 365 $\pm$ 60 days
- 18 month: Day 545 $\pm$ 60 days
- 24 month: Day 730 $\pm$ 60 days

At each study visit, the following procedures will be completed and these data recorded in source documentation and on the eCRF:

- Surgical Pain Scale -VAS
- Carolinas Comfort Scale®
- SF-12®
- Physical exam to check for hernia recurrence and surgical complications.
  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. Note: If the subject undergoes imaging for any reason and a recurrent hernia is identified, it must be recorded.
- Concomitant pain medication usage (all pain medication will be captured at baseline and all follow-up visits.
- Assessment of AEs/complications

6.3.4 Unscheduled Visits

If the subject has an evaluation related to the abdomen or abdominal organs at any time during the study follow-up period, the subject will undergo unscheduled visit study procedures (see Table of Study Events).

6.4 TABLE OF STUDY EVENTS

Study Procedure	Screening and Baseline Period	Baseline	Surgery	1 Month Visit	3 Month Visit	6 Month Visit	12 Month Visit	18 Month Visit	24 Month Visit	Unscheduled Visit/Early Termination
Visit Window (days)	**Within 60 days of consent**	**Within 7 days of surgery**	**0**	**30 ± 7**	**90 ± 30**	**180 ± 30**	**365 ± 60**	**545 ± 60**	**730 ± 60**	**--**
Describe study to potential subject	**X**									
Obtain informed consent	**X**									
Verify eligibility criteria	**X**		**X**[1]							
Pregnancy Test for WOCBP[3] (urine or serum)		**X**								
Collect demographics and medical history	**X**									
Conduct physical examination	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Placement of Device			**X**[2]							
Surgical Pain Scale (VAS)	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Carolinas Comfort Scale®	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**
SF-12®	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Collect adverse events/ complications			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Collect pain medication usage	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Schedule next follow-up visit	**X**		**X**	**X**	**X**	**X**	**X**	**X**		

[1] Verification of eligibility against inclusion/exclusion criteria prior to device placement
[2] See Section 6.2 for surgical procedure details
[3] WOCBP- Women of Childbearing Potential

6.5 **Withdrawal and/or Early Termination**

Subjects will be informed that they have the right to withdraw from the study at any time, without affecting their future care.

Additionally, subjects may be discontinued for reasons including, but not limited to the following:

- Consent is withdrawn
- Lost to follow-up (LTFU)
- Investigator withdrawal of subject
- Other

A subject is considered LTFU if the investigational site personnel are unable to locate the subject despite two documented attempts to notify the subject via telephone and a third attempt by certified mail.

A subject is considered an Early Termination (ET), if discontinuation occurs after successful implant of the study device. The site should attempt to bring the subject back to complete all ET visit study procedures (see Table of Study Events).

A subject who receives a re-operation due to hernia recurrence or has the repair site surgically impacted in any way, may be withdrawn from the study upon discharge from the most recent hospitalization. Site personnel will be responsible for documenting adverse events and other post-procedural complications on the applicable eCRF that the subject may have encountered during the hospitalization and up to 30 days post re-operation.

Once a subject discontinues from the study, the Investigator must complete a Study Completion eCRF and the reason for subject discontinuation must be fully documented.

7 STATISTICAL METHODS

This section describes the planned statistical analyses for this study. A detailed Statistical Analysis Plan (SAP) will be completed and placed on file prior to database lock. The SAP will contain a comprehensive explanation of the methodology used in the statistical analyses described below.

7.1 **Study Hypothesis**

There is no formal statistical hypothesis for this observational post-market study. The study will follow eligible, high risk patients implanted with the Phasix™ ST for hernia repair in order to assess SSO.

7.2 **Sample Size Considerations**

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.

7.3 **Data Analysis**

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 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 deviation. The protocol deviations that are considered to have a "major" grade will be defined a priori in the analysis plan. All analyses will be primarily based on the mITT population. Primary analyses may be performed for PP population as well.

Demographics and baseline characteristics will be summarized using the ITT population. Summary statistics for categorical variables will include frequency counts and percentages and for continuous variables mean, standard deviation, minimum, median and maximum.

The primary endpoint of SSO within 45 days post-implantation will be reported by visit along with the 95% confidence intervals based on the mITT population. The calculation of rates at each time point will be based on available data at the time point. Missing data will not be imputed. Additionally, a Kaplan-Meier survival analysis will be performed.

The secondary endpoints of SSO > 45 days post-implantation, hernia recurrence rate, pain – VAS, device related adverse event incidence, rate of reoperation due to the index hernia repair, Quality of life assessments (Surgical Pain Scale -VAS, Carolinas Comfort Scale® and SF-12®), surgical procedure time as measured from incision to closure (skin to skin) and length of stay will be summarized based on the mITT population with mean, standard deviation, minimum, median and maximum presented by visit. Other secondary endpoints will be summarized as appropriate.

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

Exploratory analyses on subpopulations may be performed. Interim analyses may be conducted during the study for data review purpose.

8 ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. All AEs that occur

during the study should be treated with established standards of care that will protect the life and health of the study subjects.
AEs will be collected from the time of enrollment (AE onset after signing ICF) through the end of study participation (either study completion 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

8.1 **Definition of Adverse Events**

In this study, an AE is defined as any undesirable clinical event occurring in the abdominal space including the lower abdominal, inguinal and pubic regions (including the skin), as well as any other undesirable clinical events judged to be related to the study device or surgical procedure regardless of anatomical region. Abnormal laboratory results are not to be considered AEs unless the results are accompanied by clinical signs or symptoms. The Investigator will assess the relationship of an AE to the study device or procedure as described in Section 8.5.

8.2 **Definition of Serious Adverse Events**

An event will be classified as a serious adverse event (SAE) if it meets the definition of serious injury in the Medical Device Reporting Regulation [21 CFR 803.3] as listed below:

- results in, or contributes to, a death or serious injury;
- is life-threatening (i.e., the subject was at risk of death at the time of the event);
- requires in subject hospitalization or prolongation of existing hospitalization;
- results in persistent disability or incapacity (i.e., permanent impairment of a body function or permanent damage to a body structure);
- necessitates medical or surgical intervention to prevent one of the outcomes listed above in this definition (i.e., to preclude permanent impairment of a body function or permanent damage to a body structure)

NOTE: The term serious is not synonymous with severity, which may be used to describe the intensity of an event experienced by the subject.

8.3 **Relationship of Adverse Event to Device/Procedure**

Assess each AE for its relationship to the device (Phasix™ ST) or surgical procedures as follows:

- Device: This category should be restricted to AEs directly attributable to devices used as part of the study procedure.

- Procedure: This category should be restricted to AEs directly attributable to the study device surgical procedure.

Use the following categories for assigning the certainty of the relatedness:

- Definitely Related: An AE is definitely related if it is obvious, certain or there is little doubt regarding the relationship.

- Possibly Related: An AE is possibly related if it is capable of being related but relatively unlikely.

- Not Related: An AE is not related if it is determined that there is no plausible association.

8.4 **Severity of Adverse Events**

Each AE should be assessed for its severity, or the intensity of an event, experienced by the subject.

- Mild: Awareness of a sign or symptom that does not interfere with the subject's activity or is transient and is resolved without treatment or sequelae.

- Moderate: May interfere with the subject's activity and require additional intervention and/or treatment, and may have additional sequelae.

- Severe: Significant discomfort to the subject and/or interferes with the subject's activity. Additional intervention and/or treatment are necessary. Additional sequelae occur. Severe is used to describe the intensity of an event experienced by the subject.

8.5 **Reporting Of Adverse Events**

If an AE occurs, all sections of the appropriate eCRF must be completed.

All Investigator-judged device-related AEs that occur (whether serious or not) must be reported to Davol Inc. Field Assurance using the contact information provided in Section 9, within 24 hours of becoming aware of the event.

Additionally, all SAEs (whether device- or procedure-related or not) must be reported to the Davol Study Team within 24 hours of becoming aware of the event.

It is the responsibility of the Investigator to inform the Institutional Review Board (IRB) of AEs according to IRB requirements. The Sponsor will report to the Food and Drug Administration (FDA) as appropriate after becoming aware of a reportable event.

9 MECHANICAL FAILURES, MALFUNCTIONS AND DEFECTS

The Investigator will record if a Sponsor device used in the study procedure failed to meet its performance specifications whether due to mechanical failure, malfunction or defects. This applies to: devices used in the subject, devices in which the package was opened but the device was not used for implantation in the subject, or devices with which implantation was attempted, but the device did not remain (was not used) in the subject.

A recurrence (unless it is in a different location than the study hernia) is considered a device failure if the recurrence is considered to be possibly device related, and not procedure related or an issue of patient mismanagement (e.g., mesh used was too small to adequately cover the defect, too much tension, etc.), as determined by the Investigator.

All mechanical failures, malfunctions, missing components, or any other defect of the study device or any components of the device kit that do not perform to specifications must be promptly reported to Davol:

Field Assurance Department
E-mail: Davol.FieldAssurance@crbard.com

The event must also be documented on the Device Failure eCRF and the malfunctioning device should be retained for return and evaluation to Davol Field Assurance.

10 CASE REPORT FORMS

The Investigator is responsible for ensuring the accuracy and completeness of all study documentation. All clinical study data will be recorded in the eCRFs provided to the investigational site.

11 RISK/BENEFIT ANALYSIS

Subjects participating in this study will require hernia repair surgery as part of their standard of care. The device utilized in this study is commercially available, has 510(k) clearance from the US FDA and will be used in accordance with the indications in labeling which are in effect during the study period. This study will not pose any additional potential risk to the health, safety, or welfare of the subject. The risks associated with hernia repair and Phasix™ ST may include, but are not limited to, seroma, adhesion, hematoma, pain, infection, inflammation, allergic reaction, hemorrhage, extrusion, erosion, migration, fistula formation and recurrence of the hernia or soft tissue defect.

There is no immediate benefit to the subject for participation in this study. Collection and analysis of the data generated in this study may be of benefit to future subjects who require hernia repair.

12 ADMINISTRATIVE REQUIREMENTS

This study will be conducted in accordance with the Declaration of Helsinki, HIPAA requirements, Good Clinical Practices (GCP), and applicable FDA regulations (21 CFR parts 50, 54, 56 and will be exempt from the requirements of 21 CFR part 812, as per 21 CFR part 812.2(c)(2), as the device has been cleared by the FDA for commerce and will be used as per the IFU.

12.1 **Publication Policy**

At the conclusion of the study, a multi-center article may be prepared for publication in a scientific journal. The publication of the principal results from any single-center experience within the study is not allowed until the preparation and publication of the multi-center results. Exceptions to this rule require the prior approval of Davol. The analysis of other pre-specified and non-pre-specified endpoints will be performed by Davol or its designee. Such analyses, as well as other proposed investigations will require the approval of Davol. Davol anticipates the possibility of secondary manuscripts with principal authorship. For purposes of timely abstract presentation and publication, such secondary publications will be delegated to the appropriate principal authors, and final analyses and manuscript review for all multi-center data will require the approval of Davol.

12.2 **Investigator Selection**

The Investigator must be of good standing as an Investigator and knowledgeable in relevant areas of clinical research to ensure adherence to the requirements of the protocol, including the protection of human subjects. Other site personnel must have appropriate research experience and infrastructure to ensure adherence to the protocol and enrollment of sufficient numbers of evaluable subjects. The curriculum vitae (CV) of the Investigator will be maintained in the Sponsor files as documentation of previous medical training, and federal databases will be searched to ensure that the Investigator and/or the site are not prohibited from engaging in federally Sponsored clinical research. The Principal Investigator will sign the signature page of this protocol, agreeing to comply with all applicable government regulations and the requirements of this study.

12.3 **Regulatory and Ethical Considerations**

12.3.1 Institutional Review Board Approval

Before commencement of the study, the Investigator must provide Sponsor with written documentation of IRB approval. This approval must refer to the ICF and the study by both the title and the protocol number assigned by Sponsor. The Investigator, if a member of the IRB, is not to participate in the approval decision for this study. This non-participation should be noted in the approval letter.

The IRB must give written renewal of the original approval at least annually to continue the study. A copy of the written renewal must be provided to Sponsor.

12.3.2 Informed Consent and HIPAA Authorization

Prior to the procedure, the Investigator (or designee) must explain to each subject in layman's terms, the nature of the study, its purpose, expected duration, and the benefits and risks of study participation. Also, subjects will be informed of uses and disclosures of their medical information for research purposes and their rights to access information about them. The subjects must be informed of their rights to withdraw from the study at any time for any reason without sanction, penalty, or loss of benefits to which they are otherwise entitled, and that withdrawal from the study will not jeopardize their future medical care. After this explanation and before entering the study, the subject must voluntarily sign and date the IRB-approved ICF and HIPAA Consent Form in accordance with 21 CFR Parts 50 and 56. The subject will receive a copy of their ICF and HIPAA Consent Form.

12.3.3 Confidentiality

All information and data sent to Davol Inc. or an authorized designee concerning subjects or their participation in the study will be considered confidential. All data used in the analysis and reporting of this study will be used in a manner without identifiable reference to the subject. The Investigator consents to visits by personnel of Davol Inc. and its affiliates or designees, as well as, FDA representatives.

12.4 **Protocol Adherence and Deviations**

The study will be conducted as described in this protocol. Investigators are not permitted to deviate from this protocol except to protect patient rights, safety or well-being. Any deviations from this protocol must be documented by the Investigator. If an emergency situation arises in which the rights, safety and well-being of a subject may require immediate alternative intervention, the Investigator should act in the best interest of the subject. Sponsor and the site's IRB must be notified immediately if this occurs. This should be followed with written confirmation that describes the emergency action and outcomes, to Sponsor and per IRB reporting requirements. Protocol deviations will be reviewed during routine monitoring visits. Investigators will be required to identify preventive and corrective actions to prevent further deviations. An Investigator may be disqualified from the study for repeated and/or egregious protocol deviations.

This protocol may be amended as necessary by the Sponsor. Any protocol amendments will be documented via an incremented version of this protocol (with relevant revision history) and a "was/is" comparison table to highlight the protocol changes. Amendments to the protocol must undergo the same approval process by the Sponsor, Investigators, IRBs and regulatory authorities as the original protocol.

12.5 **Device Accountability**

Only commercially available Phasix™ ST mesh will be used. Device accountability will not be required.

12.6 **Data Collection**

The Investigator is responsible for completely and accurately recording study data in the appropriate sections of the eCRFs provided by Sponsor. The eCRFs must be signed by the Investigator or by his/her documented designee.

The Investigator is also responsible for making source documents and forms readily available for a thorough review by the study monitor at each monitoring visit. The monitor will ensure the accuracy of data recording at each investigational site by comparison to supporting source documents during periodic site visits. Adherence to proper recording of information as well as assuring that corrections are being made will also be addressed during these periodic visits.

12.7 **Subject Compensation**

To compensate subjects for their time and participation, they may receive stipends upon completion of each of the protocol specified study visits. If the subject does not complete a visit, they will not be compensated for that visit.

12.8 **Communications with the Sponsor**

Although the Investigator and his/her staff may have contact with other key individuals at the Sponsor throughout the course of the study, all communications regarding conduct of the study must be channeled through the Sponsor's clinical affairs personnel or their designees.

12.9 **Required Documentation**

An Investigator may not screen or enroll subjects until authorized to do so by the Sponsor. At a minimum, the following documentation must be received by the Sponsor prior to study commencement:

- CVs and medical licenses for the principal Investigator and sub-Investigators;

- Signed Clinical Study Agreement;
- Signed Nondisclosure Agreement;
- Signed "Protocol Signature Page" (page ii of this protocol);
- Written approval from the IRB of both the protocol and ICF;
- Signed Financial Disclosure Statement; and
- IRB Assurance of Compliance Form or equivalent.

13 SITE MONITORING

The study monitors are designated as agents of the Sponsor and are assigned to oversee the conduct and progress of the study and to be the principal communication link between the Sponsor and the Investigator.

The study monitors will be involved in Investigator selection and training, assurance of IRB approvals, and periodic on-site inspection and monitoring of sites and records, to ensure continued compliance with the protocol and adequacy of the Investigator and the facility to carry out the study. In addition, the monitor will verify that the device is being used in accordance with the protocol instructions.

The site may also be subject to a quality assurance audit by personnel of the Sponsor as well as by FDA representatives.

The monitor will perform several types of site visits during the course of the study. In all cases, the study monitor will provide a written summary of the visit, including necessary follow-up items, to the Investigator and Sponsor.

It is important that the Investigator(s) and the relevant site personnel are available during the monitoring visits, and possible audit, and that sufficient time is devoted to the process.

13.1 **Study Initiation Visit**

Before the study begins, the study monitor will visit the site. The purpose of this visit is to review with the Investigator and staff the provisions and proper conduct of the clinical evaluation. This includes a detailed review of the protocol and eCRFs with instructions as to their completion, as well as reviewing regulations pertaining to the conduct of the clinical study. Arrangement for timely and accurate reporting of clinical data and relevant medical events will be established as well as ensuring safe and secure storage for the study devices.

The study monitor will:

- Confirm that the ICF to be used is the one approved by the IRB;
- Verify that all necessary documents are on file at the site; and
- Confirm that there are provisions to continue and maintain all documents and records throughout the study as required by GCP regulations.

13.2 **Ongoing Monitoring Visits**

The study monitor will maintain personal contact with the Investigator and staff throughout the study by telephone, e-mail, fax, mail, and on-site visits. On-site monitoring will begin after the first subjects are enrolled and continue until the study is completed. The monitoring will assure continued protocol compliance, adequate subject enrollment, accurate data reporting (including the comparison of eCRFs with subject records), device accountability (if required), and continued IRB acceptance of the study. The study monitor will evaluate and summarize the results of each visit in written reports, identifying any ongoing data problems with any study site and specifying recommendations for resolution of noted deficiencies. A formal monitoring plan will describe the planned extent of source data verification.

13.3 **Final Monitoring Visit**

At the completion of the study, the study monitor will conduct a final on-site visit. The purpose of this visit is to collect all outstanding study data documents, confirm that the Investigator's files are accurate and complete, review the record retention requirements with the Investigator, provide the return of unused devices (if required) to the sponsor, review records which account for device shipment (if required), and assure that all applicable requirements for closure of the study are met. The actions and observations made at this visit will be recorded and filed.

14 TERMINATION OF STUDY

Sponsor reserves the right to suspend enrollment or terminate the study at any time as set forth in the Clinical Study Agreement. Written notice will be submitted to the Investigator in advance of such termination.

Sponsor may suspend enrollment or terminate the study at a specific site for reasons including, but not limited to, inadequate data collection, low subject enrollment rate, achievement of the total enrollment, or non-compliance with the protocol or other clinical research requirements.

15 REPORTING REQUIREMENTS

The Investigator must promptly report to Sponsor any withdrawal of IRB approval at the site. Additional reporting requirements of the Investigator include:

- Reporting all ICF violations to the IRB
- Reporting all device related AEs to Davol Field Assurance Department
- Reporting all SAE to the Davol Clinical Team

16 RECORD RETENTION

The investigator shall retain all study records for a period of 2 years after the investigation is terminated or completed, or until the records are no longer required as determined by the Sponsor. The investigator may withdraw from the responsibility to maintain records for the period required and transfer custody of the records to any other person who will accept responsibility for retaining them with pre-approval. Notice of a transfer shall be given to the Sponsor not later than 10 working days after transfer occurs.

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18 APPENDICES

Appendix 1: Lead Principal Investigator

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Wilmington, NC 28401
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Appendix 2: Surgical Site Infection Classification[24]

Superficial Incisional Surgical Site Infections (SSI)

Infection occurs within 30 days after the operative procedure (where day 1 = procedure day)
AND
involves only the skin or subcutaneous tissue of the incision
AND
at least ***one*** of the following:

A. Purulent drainage from the superficial incision or subcutaneous tissue.
B. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
C. Superficial incision that is deliberately opened by a surgeon, attending physician or other designee and is culture positive or not cultured
   AND
   Patient has at least one of the following signs or symptoms: pain or tenderness; localized swelling; erythema; or heat. A culture negative finding does not meet this criterion.
D. Diagnosis of a superficial incisional SSI by the surgeon or attending physician or other designee.

COMMENT: There are two specific types of superficial incisional SSIs:

1. Superficial Incisional Primary (SIP) –a superficial incisional SSI that is identified in the primary incision in a patient that has had an operation with one or more incisions (e.g., C -section incision or chest incision for CBGB)
2. Superficial Incisional Secondary (SIS) – a superficial incisional SSI that is identified in the secondary incision in a patient that has had an operation with more than one incision (e.g., donor site incision for CBGB)

The following do not qualify as criteria for meeting the definition of superficial SSI:

- Diagnosis/treatment of cellulitis (redness/warmth/swelling), by itself, does not meet criterion d for superficial incisional SSI. An incision that is draining or culture (+) is not considered a cellulitis.
- A stitch abscess alone (minimal inflammation and discharge confined to the points of suture penetration).

Deep Incisional SSI

Infection occurs within 90 days after the operative procedure (for herniorrhaphy)(where day 1 = procedure day)
AND
involves deep soft tissues of the incision (e.g., fascia and muscle layers)
AND
patient has at least ***one*** of the following:

a. Purulent drainage from the deep incision.

b. A deep incision spontaneously dehisces or is deliberately opened or aspirated by a surgeon, attending physician or other designee and is culture positive or not cultured
AND
patient has at least ***one*** of the following signs or symptoms: fever (>38°C), localized pain or tenderness. A culture negative finding does not meet this criterion.
c. An abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test.

COMMENTS: There are two specific types of deep incisional SSIs:

1. Deep Incisional Primary (DIP) –a deep incisional SSI that is identified in a primary incision in a patient that has had an operation with one or more incisions (e.g., C-section incision or chest incision for CBGB)
2. Deep Incisional Secondary (DIS) – a deep incisional SSI that is identified in the secondary incision in a patient that has had an operation with more than one incision (e.g., donor site incision for CBGB)

Organ/Space SSI
Must meet the following criteria:
Infection occurs within 90 days after the operative procedure (for herniorrhaphy)(where day 1 = procedure day)
AND
infection involves any part of the body deeper than the fascial/muscle layers, that is opened or manipulated during the operative procedure
AND
patient has at least ***one*** of the following:
a. purulent drainage from a drain that is placed into the organ/space (e.g., closed suction drainage system, open drain, T-tube drain, CT guided drainage)
b. organisms isolated from an aseptically-obtained culture of fluid or tissue in the organ/space
c. an abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test
AND
meets at least ***one*** of the organ/space infection site "intraabdominal" criteria:
1. Patient has organisms cultured from abscess and/or purulent material from intraabdominal space.
2. Patient has abscess or other evidence of intraabdominal infection on gross anatomic or
histopathologic exam.
3. Patient has at least two of the following signs or symptoms: fever (>38.0°C$^{\pm}$), nausea*, vomiting*, abdominal pain*, or jaundice*

And at least one of the following:
a. organisms seen on culture or Gram stain of drainage or tissue obtained during invasive procedure or from an aseptically-placed drain (e.g., closed suction drainage system, open drain, T-tube drain, CT guided drainage)

b. organisms cultured from blood and imaging test evidence suggestive of infection (e.g., ultrasound, CT scan, MRI, radiolabel scans [gallium, technetium, etc.] or on abdominal x-ray), which if equivocal is supported by clinical correlation.

* With no other recognized cause
± As documented in the medical record

Appendix 3: Surgical Wound Classification[23]

- Class I/Clean: An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet the criteria.

- Class II/Clean-Contaminated*: An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.

- Class III/Contaminated*: Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered including necrotic tissue without evidence of purulent drainage (e.g., dry gangrene) are included in this category.

- Class IV/Dirty-Infected*: Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

* NOTE: In this study, subjects with Class II, Class III and Class IV wounds are to be excluded from enrollment.

Appendix 4: Routine Culture[25]

BASIC GUIDELINES FOR COLLECTION

1. Collect the material from the site in which the etiologic agent will most likely be found.

2. Obtain cultures prior to administration of antibiotics whenever possible.

3. Collect adequate volume of material. Inadequate amounts of specimen may yield false negative results.

4. Collect specimen in a manner that minimizes or eliminates contamination from indigenous flora as possible to ensure that the sample will be representative of the infected site.

5. Use appropriate collection devices, transport media, and sterile, leak proof containers.

6. Use sterile equipment and aseptic technique to collect specimen to prevent introduction of microorganisms during invasive procedures.

7. Clearly label the specimen including specific information regarding site of collection (e.g., blood obtained via blue lumen of right subclavian central catheter) and complete the ordering process.

8. Identify the specimen source and/or specific site correctly so that proper processing methods and culture media will be selected by the laboratory personnel.

9. Deliver the specimen promptly to the laboratory. Delay in transport may compromise the specimen.

SUBCUTANEOUS AND SKIN SPECIMEN:

A. Superficial Wound (bacterial)
   1. Syringe **aspiration** is preferable to swab collection.

   2. Disinfect the surface of the wound with 70% alcohol followed by povidone-iodine or povidone-iodine alone. Allow the skin disinfectant to dry prior to collection the specimen. Remove iodine with alcohol after procedure to prevent irritation.

3. Using a 3 – 5 ml syringe with a small gauge needle, a physician will aspirate the deepest portion of the lesion. If a vesicle is present, collect both fluid and cells from the base of the lesion.

4. If the initial aspiration fails to obtain material, inject sterile, preservative-free saline subcutaneously then repeat aspiration if necessary.

5. If no material is obtained, rinse needle and syringe with broth by drawing the culture medium through the needle into the syringe.

WOUNDS, ASPIRATES, AND TISSUE SPECIMEN:

A. Deep Wounds or Abscesses:

1. Disinfect the surface with 70% alcohol and a povidone-iodine solution. Remove iodine with alcohol after procedure to prevent irritation.

2. Aspirate the deepest part of the lesion, avoiding contamination by the wound surface. If collection is done at surgery, a portion of the abscess wall should also be sent for culture.

B. Punch Biopsy:

1. Disinfect the skin surface with 70% alcohol and then with a povidone-iodine solution. Remove iodine with alcohol to prevent irritation.
2. Collect 3 – 4 mm sample with a dermal punch.
3. Submit for culture in a sterile container without formalin.
4. Place specimen onto a sterile gauze pad moistened with preservative-free saline in order to keep the specimen from drying.

C. Soft Tissue Aspirate

1. Disinfect the skin surface with 70% alcohol and then with a povidone-iodine solution. Remove tincture of iodine with alcohol to prevent irritation.

2. Aspirate the deepest portion of the lesion or sinus tract. Be careful to avoid contamination by the wound surface.

Appendix 5: 2014 Joslin Clinical Guideline for Adults with Diabetes

Diabetes Mellitus – Diagnostic Criteria (Non-Pregnant Adults)

Random plasma glucose >200 mg/dl and symptoms of diabetes (polyuria, polydipsia, ketoacidosis, or unexplained weight loss)

OR

Fasting plasma glucose (FPG)* >126 mg/dl

OR

Results of a 2-hour 75-g Oral Glucose Tolerance Test (OGTT)* >200 mg/dl

OR

Glycated Hemoglobin (A1C)>6.5%**

*These tests should be confirmed by a repeat test, on a different day, unless unequivocally high
** Only an A1C test that has been referenced to an accepted laboratory method (standardized) should be utilized for diagnostic purposes