CLINICAL STUDY PROTOCOL

Title:	**A Post-Market, Prospective, Multicenter, Single-Arm Trial of XenMatrix™ AB Surgical Graft in All CDC Wound Class Ventral or Incisional Midline Hernias**
Protocol Number:	**DVL-HE-012**
Study Type:	**Post-Market**
Date:	**August 7, 2018**
Version:	**3.0**
Study Device:	**Bard[文] XenMatrix™ AB Surgical Graft**
Sponsor:	**Davol Inc.** **Subsidiary of C. R. Bard, Inc.** **100 Crossings Boulevard** **Warwick, RI 02886** **Phone: 1-800-556-6756**
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NCT number: NCT02691962
NCT number added post approval as per CT.gov requirement.

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
ADL	Activities of Daily Living
AE(s)	Adverse Event(s)
AMP	Antimicrobial Prophylaxis
ASA	American Society of Anesthesiology
Bard	C. R. Bard, Inc.
BMI	Body Mass Index
CDC	Centers for Disease Control
C. difficile	Clostridium difficile bacterium
CFR	Code of Federal Regulations
cm	Centimeter
COPD	Chronic Obstructive Pulmonary Disease
CST	Component Separation Technique
CT	Computed Tomography
CV	Curriculum Vitae
E. aerogenes	Enterobacter aerogenes bacterium
E. Coli	Escherichia coli bacterium
eCRF(s)	Electronic Case Report Form(s)
e.g.	For example
etc.	Et cetera, and others
F	Fahrenheit
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
i.e.	Id est, that is
IFU	Instructions for Use
Inc.	Incorporated
IRB	Institutional Review Board
ITT	Intent-to-Treat
kg	Kilogram
LTFU	Loss/Lost to Follow-up
m	Meter
mg / dL	Milligrams per deciliter
mITT	Modified Intent-to-Treat
MRI	Magnetic Resonance Imaging
MRSA	Methicillin-resistant Staphylococcus aureus
N	Number
POD	Post-operative Day
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SCIP	Surgical Care Improvement Project
SF-12	Short-Form-12

TAR	Transversus Abdominis Release
U.S.	United States
USDA	United States Department of Agriculture
V.A.C.®	Vacuum-Assisted Closure
XenMatrix™ AB	XenMatrix™ AB Surgical Graft (device) or surgical graft

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1. INTRODUCTION

1.1. Background

With more than 2 million abdominal operations performed annually in the United States (U.S.) and with up to 20% of those patients developing ventral or 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 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% recurrence rate. [4-7] Primary suture repair has been nearly abandoned for the repair of hernias which are greater than five centimeters (cm) in size. [4-7] As a result, many ventral hernia repair procedures involve the use of a mesh material.

Synthetic mesh repair procedures, either open or laparoscopic, have been reported to lead to fewer recurrences compared to primary repairs. [8-11] Improved outcomes with mesh are believed to be related to better distribution of tension on the fascial edges and sutures when mesh is used in hernia repair procedures. [41] However, complex cases and large abdominal wall defects continue to pose a challenge to surgeons. [32] 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, 30] These large abdominal wall defects have been associated with recurrence rates of up to 46%. [13]

Today many surgeons prefer to close large defects primarily and then reinforce the primary repair with biologic or synthetic mesh. In order to close these large defects surgeons rely on one of several component release techniques. One approach to addressing the complexity of large abdominal wall defect (>5 cm in width) repair is the Component Separation Method. The method was developed by Ramirez et al. in 1990 and was based on the assumption that separating the muscle components of the abdominal wall would allow mobilization of the entire abdominal wall as a complete unit, allowing the surgeon to bring the midline together with less tension, thus allowing better repair of large abdominal wall defects. [14] Numerous variations on the original component separation method have emerged and have reported recurrence rates from 0% to 30%.[14-19] These variations range from procedural technique, selection and use of prosthetic repair material, and location of placement of such material. Preliminary results suggest minimally invasive techniques may be

associated with fewer complications; however, there are similar recurrence rates between laparoscopic and open repair. [4, 20, 35]

Although positive outcomes have been reported with the component separation technique when used with synthetic mesh, the presence of a permanent foreign body material may be associated with persistent wound infection, fistula formation, seroma development, mesh contraction and migration, visceral erosions, adhesions, chronic pain and foreign body reactions. [29]

The reported risk of a wound infection following ventral hernia repair ranges between 0% and 23%. [11, 21-28] Deep mesh infection frequently results in major complications including, the need for repeat surgery with or without mesh removal, wound dehiscence, prolonged recovery, decreased patient quality of life, and extended long-term hospitalization. [29]

Biologic grafts provide a temporary collagen scaffold which is remodeled and replaced with the body's own tissue over time to repair a hernia defect with fewer postoperative chronic wound complications. [33-35] These grafts aim to address many of the deficiencies of synthetic mesh, such as the need for additional surgery to remove infected permanent mesh in the event of surgical site infection while preserving the positive attributes of strength and the potential for durable, definitive hernia repair. [8, 36, 39]

Risk of surgical site infection has been defined and categorized in the Centers for Disease Control's (CDC) Guidelines for the prevention of surgical site infection published in 1999 (see Table 1). [49] This classification system has provided conformity in the definitions used to classify and categorize general surgical site infections (see Table 1).

Table 1: Center for Disease Control's Surgical Wound Classification System

Class	CDC Surgical Wound Classification[49]
I	Clean: An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract are 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.
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.
III	Contaminated: Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage

Class	CDC Surgical Wound Classification[49]
	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.
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.

The ability of biologic grafts to support revascularization and in growth of new cells may contribute to the clearance of bacteria. [4] Some biologic grafts have been shown to remain intact in the setting of active infection without requiring removal when exposed or infected. [31, 40, 43, 45-47] Additionally, some clinical reports note patients were able to be managed non-surgically even when the patients' wounds became infected. [31, 38, 45-47]

In addition to selecting specific hernia repair materials, surgeons give consideration to the placement of repair material as there is evidence that the anatomical location of the graft is important. There are three general locations for placing the graft, including onlay, inlay, and underlay positions, and most have found the underlay technique to be the better technique when complete fascial closure can be achieved based on the lower rate of re-herniation. [4] It is believed that intra-abdominal forces are distributed more evenly across the repair material when placed in the underlay position as the intra-abdominal pressures push the repair material into the defect and against the native tissue rather than away from the defect. [4, 42]

1.2. Rationale

This study aims to prospectively explore the use of XenMatrix™ AB Surgical Graft for ventral or incisional midline hernia repair in patients across all wound classes ("All Comers") through 24 months post repair.

The device that will be utilized in this study (XenMatrix™ AB Surgical Graft) is intended for implantation to reinforce soft tissue where weakness exists and for surgical repair of damaged or ruptured soft tissue, including: abdominal plastic and reconstructive surgery; muscle flap reinforcement; hernia repair including abdominal, inguinal, femoral, diaphragmatic, scrotal, umbilical, and incisional hernias. The Rifampin and Minocycline coating has been shown in preclinical in vitro and in vivo testing to reduce or inhibit microbial colonization on the device. The claim of reduction of bacterial clearance of the device has not been established with human clinical data, nor has a clinical impact associated with this claim been demonstrated.

Preclinical in vivo studies demonstrated an average of 4 log reduction of microbial colonization against gram-positive Methicillin-resistant Staphylococcus aureus

(MRSA) and an average of 4 log reduction against gram-negative Escherichia coli (E. coli). In vitro speed-to-kill testing demonstrated a minimum 4 log reduction against gram-positive MRSA and Methicillin-resistant Staphylococcus epidermidis (MRSE) and gram-negative Enterobacter aerogenes (E. aerogenes) and E. coli. [48] These preclinical efficacy results cannot be considered predictive of clinical performance. Clinical studies to evaluate performance and risk of infection have not been performed.

1.3. Device Description

XenMatrix™ AB Surgical Graft is an acellular, sterile, non-pyrogenic porcine dermal matrix packed dry for use in the reconstruction of soft tissue deficiencies. The device surfaces are coated with the antibacterial agents Rifampin and Minocycline in a bioresorbable L-Tyrosine succinate polymer carrier. The product has an orange surface and minor non-uniform color variation on the product surface ("freckles") that is normal.

The coating is shaded orange in color from the antimicrobial agents. In preclinical in vitro and in vivo testing, the antimicrobial agents reduce or inhibit microbial colonization of the product during the initial healing process for up to 7 days following surgery. Absorption of the resorbable polymer carrier for the antimicrobials is complete in approximately 12 months.

2. STUDY OBJECTIVES

The objective of this study is collect data on the performance and use of XenMatrix™ AB Surgical Graft for up to 24 months in subjects with ventral or incisional midline hernias, across all CDC wound classes in the retro-rectus or intraperitoneal location.

3. STUDY ENDPOINTS

3.1. Primary Endpoint

1. Wound Occurrences in the first 45 days post-implantation.
   Wound Occurrences will be defined as surgical site infection, seroma, wound dehiscence, skin necrosis and fistulas requiring intervention

3.2. Secondary Endpoints

The secondary endpoints of this study are as follows:

1. Wound Occurrences >45 days post-implantation

2. Rate of hernia recurrence
3. Rate of reoperation due to the index hernia repair
4. Carolinas Comfort Scale® and SF-12®
5. Return to Work
6. Length of Stay

4. STUDY DESIGN

This is a prospective, multicenter, single-arm clinical study to collect data on the performance and use of XenMatrix™ AB Surgical Graft for ventral or incisional midline hernia repair across patients in all CDC wound classes utilizing retro-rectus or intraperitoneal placement of mesh. The study will be conducted at approximately 10 U.S. sites to treat approximately 75 subjects. Follow-up visits will be conducted at 1, 3, 6, 12, 18 and 24 month(s) 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 enroll up to 75 subjects at approximately 10 sites.

5.2. Eligibility Criteria

5.2.1. Inclusion Criteria

1. Subject must be ≥18 years of age.
2. Subject must be willing and able to give written informed consent.
3. Subject must be diagnosed with a ventral or incisional midline hernia.
4. Mesh must be placed in the retro-rectus or intraperitoneal plane.
5. Subject must be willing to undergo open hernia repair and be able to undergo all other study procedures as outlined in this protocol.

5.2.2. Exclusion Criteria

1. The use of surgical graft as a bridge repair.
2. The subject has more than 4 prior recurrences.
3. Subject has a contraindication for the placement of surgical graft.
4. Complete removal of existing mesh from a prior hernia repair (in the same affected area) is not possible.
5. The study hernia repair requires more than a single piece mesh (including sufficient overlap beyond margins of the defect on all sides).

6. Subject has intact permanent mesh adjacent to the current hernia to be repaired.
7. Subject has peritonitis at the time of surgery.
8. The subject is an active smoker within the last 2 weeks prior to surgery.
9. Clinically significant COPD or heart failure, defined as marked limitation in ability or inability to perform activities of daily living.
10. Subject had chemotherapy within the last 12 months, is on or suspected to be placed on chemotherapy medications during any part of the study.
11. Chronic steroid use (>6 months) or immunosuppression drugs.
12. Subject's body mass index (BMI) >45 kg/m^2.
13. Subject has cirrhosis, and/or ascites.
14. Subject has a defined collagen disorder.
15. Known to be infected with human immunodeficiency virus (HIV).
16. Subject has clinically significant (not based solely on creatinine levels) kidney disease that limits ADL, is on hemodialysis or peritoneal dialysis.
17. Subject is American Society of Anesthesiology (ASA) Class 4 or 5.
18. Subject has a life expectancy < 2 years at the time of enrollment.
19. Subject is pregnant, breastfeeding or planning on becoming pregnant during the course of the study.
20. Subjects with known sensitivity to porcine products.
21. Subjects with allergy, history of allergy or hypersensitivity to tetracyclines (including minocycline) or rifamycins (including rifampin).
22. Subject has any condition in the opinion of the Investigator that would preclude the use of the study device, or preclude the subject from completing the follow-up requirements.

6. STUDY PROCEDURES

6.1. Subject Screening And Baseline Evaluation

Subjects with a diagnosis of ventral or incisional midline hernia requiring surgical repair will be screened for eligibility against the study protocol inclusion and exclusion criteria utilizing ordinary standard of care procedures (e.g., limited physical examination typical for hernia patients, blood work (if necessary), medical evaluation, etc.) which occurred within 60 days of the date of consent. 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 Investigators 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 specific procedures will be conducted and documented:

6.1.1. Informed Consent

All subjects or legally authorized representatives will provide written informed consent for the study prior to collection of study data or performance of study procedures. A signed copy of the informed consent form (ICF) must be given to the subject.

6.1.2. Enrollment

Subjects who sign an informed consent will be considered provisionally enrolled until all eligibility criteria have been successfully met, at which time subjects will be considered formally enrolled. Subjects who do not meet all eligibility criteria will be considered screen failures.

6.1.3. Eligibility

The subject's eligibility for study enrollment will be reviewed and documented on the appropriate electronic case report form (eCRF). At the time of screening, a related progress note should be recorded in the medical records to indicate that all study eligibility criteria were reviewed with the screening results noted.

Subjects who fail to meet eligibility criteria should be treated according to the Investigator's standard of care practices. Study participation will end at the time of eligibility failure. Data will be collected for all subjects who fail to meet eligibility criteria from the time the informed consent is signed until the subject is determined to have failed screening. At a minimum, the following information should be collected for all subjects who fail to meet study eligibility criteria:

- Subject demographics
- Reason for screen failure
- Serious adverse events (followed until resolution or stabilization)

6.1.4. Assignment of Subject Number

A unique identification number will be given to each study subject at the time the subject provides informed consent. Subject numbers will be assigned in a sequential

order. The subject number will consist of six digits where the first three digits designate the study site and the last three digits designate the subject by number in sequential order.

6.1.5. Demographics And Medical History

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

Medical history information will include a review of ventral or incisional hernia related events and details (including previous interventions) and location of hernia, and previous abdominal surgery.

6.1.6. 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.

6.1.7. Quality of Life Assessment

Subjects will complete the Carolinas Comfort Scale® and SF-12® to establish baseline measures for quality of life assessments. Occupational status will also be collected.

6.2. Index Procedure

The following section describes the surgical techniques that are recommended for this study. Since bridging a defect with a graft is not allowed, several release techniques are recommended; however, other surgical techniques may be applied at the surgeon's discretion. Sponsor representatives may attend the index procedures conducted under this protocol.

6.2.1. Perioperative Care

Since the lowest incidence of post-operative infection is associated with administration of an antibiotic within one hour prior to incision, prophylactic antibiotics are to be administered within one hour prior to surgery (first skin incision) and two (2) hours before if the antibiotic is a fluoroquinolone or vancomycin (according to the Surgical Care Improvement Program [SCIP]). [51] Prophylactic antibiotics should be discontinued less than 24 hours after anesthesia end time as prolonged administration

of antibiotics can lead to the development of antimicrobial resistant pathogens and an increased risk of C. difficile infection. [51]

6.2.2. Abdominal Wall Reconstruction/Ventral or Incisional Hernia Surgery

CDC Guidelines

Intraoperative abdominal prep is to be performed according to the nationally recognized standard, CDC Guideline for Prevention of Surgical Site Infection. [49] If not already receiving therapeutic antimicrobial agent perioperatively for an established infection, surgical antimicrobial prophylaxis (AMP) should be given just before the operation begins and timing should be based on surgeon practice but, at a minimum, until bactericidal concentration of the drug in serum and tissues is established by the time the skin is incised. Therapeutic levels should be maintained in both serum and tissues throughout the operation and until, at most a few hours after the incision is closed in the operating room. These guidelines are as specified in the CDC Guideline for Prevention of Surgical Site Infection. [49] The type of AMP administered will be according to hospital protocol and surgeon decision and should be documented. All perioperative and postoperative antibiotics given to the subject should be documented.

Adhesiolysis & Measurement of the Defect

Once the adhesiolysis is performed and all of the ventral or incisional hernia has been exposed, the largest vertical and transverse dimensions should be recorded.

Minimize Bioburden

Every effort should be made to minimize the bacterial burden and risk of post-operative complications including debridement of non-viable tissue, abdominal washouts, careful preservation of blood supply to the skin, and complete removal of all prior mesh (as applicable).

Ventral or Incisional Hernia Repair

If necessary, resect/debride the edges of the rectus fascia until healthy well-vascularized tissue is identified to ensure proper apposition of the midline as it is closed.

If a retro-rectus approach is preferred and the midline can be closed primarily, the peritoneum or posterior rectus sheath should be carefully dissected creating a retro-rectus pocket for the XenMatrix™ AB Surgical Graft to be placed.

If further release is needed to close the midline every effort should be made to do so including the use of the TAR technique [50]. Care must be taken not to damage the blood supply and the nerves. Once the dissection is complete the peritoneum/ posterior rectus sheath should be closed and the XenMatrix™ AB graft should be placed in the retro rectus space according to the instructions for use (IFU).

If intraperitoneal graft placement is preferred (and the midline can be closed by any means (including CST)), place the graft intraperitoneally and close the fascial edges of the defect anterior to graft.

The defect will be closed and a minimum 5 cm overlap on every side should be factored in to determine the minimal patch size. The entire defect must be covered. The patch will be fixated using sutures. If the hernia repair requires more than a single piece of surgical graft (with adequate overlap beyond the margins of the defect on all sides) the subject is excluded from the study.

Closure should be performed with permanent or long lasting sutures every 1-2 cm between sutures, for example with an interrupted Figure-8 closure or running stitch.

If a previous scar of skin is present, the scar should be excised. The fascial and subcutaneous layers should be closed with sutures. The skin should be closed with staples and/or sutures (1-2 cm between sutures preferred).

6.2.3. Immediate Postoperative Care

After surgery, study subjects will be given postoperative instructions for care of the ventral or incisional hernia repair site based on the Investigator's typical protocol. Prescription medication should be what is normally prescribed to ventral or incisional midline hernia repair study subjects. Study subjects should be asked to use prescription and non-prescription drugs on an as needed basis only.

The Investigator will determine the extent of individual activity that is appropriate, including lifting and other forms of physical exertion.

6.2.4. Surgical Details

Surgical details will be recorded and entered in the appropriate eCRF(s). Details may include but are not be limited to: ASA score, size of the defect, procedure start/stop time (skin to skin), perioperative antibiotics (including dose and timing), concomitant procedures (e.g., panniculectomy), was closure achieved (midline, fascia, skin) hospital length of stay, and adverse events including device or procedure related complications and mortality.

6.3. Subject Follow-up

Subjects who sign the informed consent and meet eligibility criteria but who do not undergo the XenMatrix™ AB Surgical Graft placement surgery per-protocol should be treated per hospital standard of care. Follow-up will end at the time it is determined that the ventral or incisional midline hernia repair surgery utilizing XenMatrix™ AB Surgical Graft was not performed as planned (i.e., prior mesh could not be removed).

However, any study-related adverse events will be reported and followed to satisfactory resolution or stabilization.

Failure of the study procedure must be documented and surgical details must be recorded on the appropriate eCRF(s).

6.3.1. Assessments

Subjects should report to their respective study site for follow-up visits at the post-operative time points below:

- 1 month: ± 2 weeks
- 3 month: ± 1 month
- 6 month: ± 1 month
- 12 month: ± 2 months
- 18 month: ± 2 months
- 24 month: ± 2 months

At each study visit, the following procedures will be completed:

- Physical exam will be performed by a study physician to check for wound occurrences, hernia recurrence and any other surgical complications. The physical exam should also include assessment of the subjects' weight and skin appearance over the ventral or incisional midline hernia repair site.
- A recurrent ventral or incisional midline hernia will be defined as any hernia identified or confirmed by the investigator, during any study follow-up visit (including unscheduled), within approximately 5 cm of the index hernia.
- Potential recurrent hernias identified via incidental magnetic resonance imaging (MRI) or computed tomography (CT) scan will be evaluated by the operating surgeon for clinical significance.
- If an infection is suspected, a routine culture shall be obtained via the instructions in Appendix 18.2. Classification will follow the CDC guidelines for superficial and deep surgical site infections in Appendix 18.3.
- Return to Work
- Carolinas Comfort Scale®
- SF-12®
- Assessment and documentation of adverse events/complications.

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

6.3.2. Unscheduled Visits

Unscheduled visits are visits in addition to the per protocol study schedule, at the request of the subject or study personnel to address intercurrent problems or concerns.

If the subject has an evaluation related to the abdomen or abdominal organs at an unscheduled visit at any time during the study follow-up period, the subject will be treated per standard of care. Any serious adverse events and/or relevant AEs should be recorded. If the subject should undergo imaging for any reason and a recurrent ventral or incisional midline hernia is identified, it must be recorded as well.

> Unscheduled Visits should only be completed in the eCRF if AEs occurred or if this is an Early Termination visit.

6.4. Time And Events Schedule

Study Procedure	Screening and Baseline Period	Surgery	1 Month Visit	3 Month Visit	6 Month Visit	12 Month Visit	18 Month Visit	24 Month Visit	Unscheduled Visit[1)]
Visit Window (days)	**Within 60 days of consent**	**0**	**16-44**	**60-120**	**150-210**	**305-425**	**485-605**	**670-790**	**--**
Describe study to potential subject	**X**								
Obtain informed consent	**X**								
Verify eligibility criteria	**X**	**X**							
Collect demographics and medical history	**X**								
Conduct physical examination	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Placement of Device		**X**							
Return to Work, Carolinas Comfort Scale®, SF-12®	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Collect adverse events/complications	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

[1)] Only to be completed in eCRF if subject experienced AE or if this is an Early Termination visit.

6.5. Subject Discontinuation

Subjects may be discontinued for the following reasons:

- Subject has device explanted.
- Subject is Lost to Follow-Up (LTFU): A subject may be 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.
- Subject consent is withdrawn: The subject requests to terminate his/her participation in the study (the Investigator must attempt to identify and document the reasons for termination). Subjects will be informed that they have the right to withdraw from the study at any time, for any reason, without affecting their future care.
- Study termination: The study is terminated by Sponsor.

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.

6.6. Replacement of Subjects

A subject that discontinues from the trial will not be replaced.

7. 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.

7.1. Definition of 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 7.3.

7.2. Definition of Serious Adverse Events (SAE)

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

- Is life-threatening,
- Results in permanent impairment of a body function or permanent damage to a body structure,
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

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

7.3. Relationship Of Adverse Event To Device/Procedure

Assess each AE for its relationship to the device (XenMatrix™ AB Surgical Graft) 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.

7.4. 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 usual activity.
- Severe: Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

7.5. Reporting Of Events

If an AE occurs, all sections of the appropriate eCRF must be completed. In addition, all AEs will be classified by the investigator according to the Clavien-Dindo Grading System for the Classification of Surgical Complications to eliminate subjective interpretation of adverse events and any tendency to down-rate complications.

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 8, within 24 hours of becoming aware of the event.

Additionally, all SAEs (regardless of relationship) must be reported to the Sponsor within 24 hours of becoming aware of the event by sending an email to XenAB@crbard.com.
This email should contain the following minimal information:
- short description of the SAE
- device/procedure relationship
- date SAE occurred
- date of awareness

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.

8. 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., use of a Vacuum Assisted Closure (V.A.C.) system for too long; graft used was too small to adequately cover the defect, etc.), as determined by the Investigator.

All mechanical failures, malfunctions, missing components, or any other defect of XenMatrix™ AB Surgical Graft, 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.

9. RISK/BENEFIT ANALYSIS

The device that will be utilized in this study (XenMatrix™ AB Surgical Graft) has 510(k) clearance from the U.S. Food and Drug Administration and is intended for implantation to reinforce soft tissue where weakness exists and for surgical repair of damaged or ruptured soft tissue, including: abdominal plastic and reconstructive surgery; muscle flap reinforcement; hernia repair including abdominal, inguinal, femoral, diaphragmatic, scrotal, umbilical, and incisional hernias.

The study subjects participating in this study will require ventral or incisional midline hernia repair surgery as part of their standard of care. The usual risks of ventral or incisional midline hernia repair apply independent of the procedures required under this protocol. The known possible risks associated with the use of the XenMatrix™ AB Surgical Graft are outlined in the IFU (attached).

Collection and analysis of the data generated in this study may be of benefit to future subjects who require ventral or incisional midline hernia repair.

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. 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.

11.1. Study Hypothesis

There is no formal statistical hypothesis for this study. The study will follow eligible patients across all CDC wound classes who undergo ventral or incisional midline

hernia repair with the XenMatrix™ AB Surgical Graft in order to assess wound occurrences.

11.2. Sample Size Considerations

This study is projected to enroll up to 75 subjects at approximately 10 sites in order to have 64 evaluable subjects at 24 months. It is anticipated that there will be a 15% loss to follow-up rate. The sample size of 64 evaluable subjects is based on potential adequacy of data to meet the study objectives. It is not based on any statistical consideration.

11.3. Data Analysis

11.3.1. Analysis Population

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 whom underwent placement of a XenMatrix™ AB Surgical Graft. Subjects who are enrolled but not treated with XenMatrix AB will be replaced to ensure 75 subjects are treated with the study device. All analyses will be primarily based on the mITT population.

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

Subjects who do not receive XenMatrix™ AB Surgical Graft will have their AEs summarized separately and their outcome data will not be collected or analyzed.

11.3.2. Primary Endpoint

The primary endpoint of wound occurrence rate will be assessed within the first 45 days post-implantation. Wound occurrences are defined as surgical site infection, seroma, wound dehiscence, skin necrosis and fistulas requiring intervention.

11.3.3. Secondary Endpoints

The following secondary endpoints will be evaluated:

1. Wound occurrences > 45 days post-implantation
2. Rate of reoperation due to the index hernia repair
3. Carolinas Comfort Scale® and SF-12®
4. Return to Work
5. Length of Stay

For each of the above listed secondary endpoints, estimates along with their 95% confidence intervals of the variable of interest based on the mITT population will be reported.

11.4. Data Analysis Considerations

11.4.1. Data pooling

Data from all investigational sites will be pooled for analysis. Sites will be tested for potential differences in the primary endpoint. Sites with fewer than 10 treated subjects will be combined for this purpose. If there is significant variation among sites, the rates of the primary endpoint and associated 95% confidence interval will be estimated using a logistic regression with sites included in the model as a random effect.

11.4.2. Handling of missing data

Study endpoints may be missing due to withdrawal of consent, investigator's decision, lost to follow-up, device explanted and death. As long as the missing data is unrelated to the study intervention, limiting the analysis to those subjects who contribute endpoints produces unbiased estimates of the event rates. The reason for missing data for all subjects will be reported. The primary analysis will be performed without imputation for the missing data. As secondary analysis, the rates of the primary endpoint will be estimated using Kaplan Meier method that will account the time at risk prior to discontinuation of the study.

11.5. Interim Analysis

An interim analysis of some or all study endpoints will be performed after all active subjects have a 12-month visit. However, interim analyses may be performed at other time periods (e.g., 6-months) to assess the results. There is no statistical impact of the interim analysis. i.e. the study will continue as originally planned and will not be affected in any way by the result of the interim analysis. All study endpoints will be summarized for 12-month follow-up at interim analysis.

12. ADMINISTRATIVE REQUIREMENTS

This clinical study will be conducted in accordance with the Declaration of Helsinki, HIPAA requirements, Good Clinical Practice, and applicable FDA regulations (21 CFR Parts 50, 54, and 56).

12.1. 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(s) will be maintained in the Sponsor files as documentation of previous medical training. Federal databases will be searched to ensure that the Investigator(s) and/or the site are not prohibited from engaging in federally sponsored clinical research. The Investigator will sign the signature page of this protocol, agreeing to comply with all applicable government regulations and the requirements of this study.

12.2. Regulatory and Ethical Considerations

12.2.1. Institutional Review Board (IRB) 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 the 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.

No device supplies, if applicable, will be shipped to the Investigator until the IRB approval has been supplied to Sponsor.

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.

As appropriate, amendments to the protocol must also be approved by the IRB before implementation at the sites, unless warranted to eliminate an immediate hazard.

12.2.2. Informed Consent and HIPAA Authorization

Prior to any study 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 risks and benefits 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 right to withdraw from the study at any time and 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 any study procedure is conducted, and before entering the study, the subject (or legally authorized representative) 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. Protocol Adherence And Deviations

The study will be conducted as described in this protocol. Any deviations from this protocol must be documented by the Investigator. If an emergency situation arises in which the safety and welfare of a subject may require immediate alternative intervention, the Investigator should act in the best interests of the subject. The Sponsor and the site's IRB must be notified immediately if this occurs. All notifications should be followed with written confirmation that describes the emergency action and outcomes. Written confirmations should be sent to Sponsor and the IRB within 10 business days from the date of the emergency action.

12.4. Device Accountability

The Investigator will ensure that the device components are stored under the conditions outlined in the IFU and maintained under secure storage. Device accountability records will be maintained and monitored. Study devices may not be re-sterilized or reused.

12.5. 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.

12.6. 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, compensation will not be provided for that visit.

12.7. Communications With The Sponsor

Although the Investigator and his/her staff may have contact with 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. The Sponsor contact listed on the title page of this protocol should be contacted first with any matters regarding the conduct of this study.

12.8. 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-Investigator(s);
- signed Clinical Study Agreement;
- signed Nondisclosure Agreement;
- signed Protocol Signature Page;
- written approval from the IRB of both the protocol and informed consent form;
- signed Financial Disclosure Statement; and,
- IRB Assurance of Compliance Form or equivalent.

12.9. Publications

At the conclusion of the Study, a multi-center journal article may be prepared for publication in a reputable 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 Bard. The analysis of other pre-specified and ad hoc endpoints will be performed by Bard or its designee. Such analyses, as well as other proposed investigations will require the approval of Bard. Bard anticipates many 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 the Bard.

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 Sponsor and 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 monitor will perform several types of site visits during the course of the study.

The investigational sites may also be subject to quality assurance audit by the Sponsor (and its affiliates) and the Sponsor's study contractor personnel, as well as by FDA representatives. It is important that the Principal Investigator and the relevant investigational

site personnel are available during the monitoring visits and possible audits 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. Arrangements 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 good clinical practice 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. This monitoring will assure continued protocol compliance, adequate subject enrollment, accurate data reporting (including the comparison of eCRFs with subject records), device accountability, 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.

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 for the return of unused devices to Sponsor, review records which account for device shipments, 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, administrative reasons, or non-compliance with the protocol or other clinical research requirements.

15. REPORTING REQUIREMENTS

This study protocol is exempt from 21 CFR 812 as the device is cleared for commercialization in the U.S. and the usage in this protocol in on-label. In addition to the AE reporting described above, all sites are also required to submit annual study progress reports to the Sponsor.

16. RECORD RETENTION

The investigator shall retain all study records for a period of two years after the latter of the following two dates: the date on which the study is terminated or completed, or the date a marketing application is approved for the indication for which it is being investigated. 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. 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

18.1. Principal Investigator Information

[redacted]

18.2. Routine Culture [56]

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 subclavia 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.

18.3. Surgical Site Infection Classification [44]

Surgical Site Infection Criteria

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

18.4. Clavien Dindo Classification [57]

Grades Definition

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as anti-emetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anesthesia
- IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
- IVa	single organ dysfunction (including dialysis)
- IVb	Multi-organ dysfunction
Greade V	Death of a patient
Suffix "d"	If the patients suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*brain hemorrhage, ischemic stroke, sub-arrachnoidal bleeding, but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit.

18.5. Instructions for Use

XENMATRIX™ AB Surgical Graft

Porcine Dermal Matrix
Coated with Rifampin and Minocycline

Instructions for Use

Single Use

Read all instructions prior to use

℞ only

Do not resterilize

STERILE EO

30°C (86°F)

Storage not to Exceed 30°C

Manufacturer:
Davol Inc.
Subsidiary of C. R. Bard, Inc.
100 Crossings Boulevard
Warwick, RI 02886 USA
1-401-825-8300 • 1-800-556-6275

Medical Services & Support
Clinical Information Line
1-800-562-0027

BARD
DAVOL INC.

PK3798261
149R

PRODUCT DESCRIPTION

XENMATRIX™ AB Surgical Graft is an acellular, sterile, non-pyrogenic porcine dermal matrix packed dry for use in the reconstruction of soft tissue deficiencies. The device surfaces are coated with the antibacterial agents Rifampin and Minocycline in a bioresorbable L-Tyrosine succinate polymer carrier. The product is designed to have a uniform orange surface and some minor non-uniform color variation on the product surface is normal.

ACTIONS

The device surfaces are coated with a bioresorbable L-Tyrosine succinate polymer which serves as a carrier for the antibacterial agents Rifampin and Minocycline, in equal concentrations of approximately 180 µg/cm^2. The coating is shaded orange in color from the antimicrobial agents. Absorption of the resorbable polymer carrier is essentially complete in approximately 12 months based on *in vitro* studies.
In preclinical in vitro and in vivo testing, the antimicrobial agents reduce or inhibit microbial colonization of the device (please see performance data section below). The claim of reduction of bacterial colonization of the device has not been established with human clinical data, nor has a clinical impact associated with this claim been demonstrated.

Preclinical effectiveness results cannot be considered predictive of clinical performance.

STORAGE

Store the XENMATRIX™ AB Surgical Graft in a dry environment and protected from direct sunlight. Store at room temperature not to exceed 30°C (86°F). It is for single use only. Do not use if the package is damaged or open.

INDICATIONS

Intended for implantation to reinforce soft tissue where weakness exists and for surgical repair of damaged or ruptured soft tissue, including: abdominal plastic and reconstructive surgery; muscle flap reinforcement; hernia repair including abdominal, inguinal, femoral, diaphragmatic, scrotal, umbilical, and incisional hernias. The Rifampin and Minocycline coating has been shown in preclinical in vitro and in vivo testing to reduce or inhibit microbial colonization in the device. The claim of reduction of bacterial colonization of the device has not been established with human clinical data, nor has a clinical impact associated with this claim been demonstrated.

CONTRAINDICATIONS

1. XENMATRIX™ AB Surgical Graft should not be used on patients with known sensitivity to porcine products.
2. Do not use in patients with allergy, history of allergy or hypersensitivity to tetracyclines or rifamycins or other components in the device.
3. Do not use in pregnant or nursing women.
4. The contraindications, warnings and precautions regarding the use of the antimicrobial agents Rifampin (a derivative of rifamycinB) and Minocycline (a derivative of tetracycline) apply and should be considered when using this device. See FDA's drug labeling database for Rifampin and Minocycline labeling. For reference the contraindications for Minocycline and Rifampin are as follows:
Contraindications for Oral Capsule (1 mg/kg) of Minocycline:
• This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.
Contraindications for both IV (600mg) and Oral Capsule (150mg-300mg) of Rifampin:
• Rifampin is contraindicated in patients with a history of hypersensitivity to Rifampin or any of the components, or to any of the rifamycins.
The use of this product in patients with compromised hepatic function should be carefully considered since Rifampin can cause additional stress to hepatic metabolism. Implantation of this device would not result in detectable systemic concentrations of Rifampin or Minocycline.
Patients implanted with the largest product size (19 cm x 35 cm) are calculated to receive a one time total dose of approximately 177 mg each of Rifampin and Minocycline. This is in contrast to typical systemic treatment doses, which are 600 mg for Rifampin and 200 mg for Minocycline administered multiple times per day, over several days to several months.
5. Not for reconstruction of cardiovascular defects.
6. Not for reconstruction of central nervous system or peripheral nervous system defects.
7. Use of this product in applications other than those indicated has the potential for serious complications.

WARNINGS

1. **This device is not indicated for the treatment of infection. If an infection develops, treat the infection aggressively.**
2. **To minimize recurrences when repairing hernias, the graft should be large enough to provide sufficient overlap beyond the margins of the defect on all sides.**
3. **Prior to use, carefully examine package and product to verify neither is damaged and that all seals are intact. Do not use if the package is damaged or open.**
4. **An allergic reaction that is unrelated to other therapy is an indication to consider removal of XENMATRIX™ AB Surgical Graft.**
5. **Do not use this product in patients with allergy, history of allergy or hypersensitivity to tetracyclines or rifamycins or other components of the device.**
6. **After use, any unused product and packaging should be treated as a potential biohazard. Handle and dispose of in accordance with accepted medical practice and applicable local, state, and federal laws and regulations.**

7. Do not resterilize. This device has been designed for single use only. Reuse, reprocessing, resterilization or repackaging may compromise the structural integrity and/or essential material and design characteristics that are critical to the overall performance of the device and may lead to device failure which may result in injury to the patient.
Reuse, reprocessing, resterilization or repackaging may also create a risk of contamination of the device and/or cause patient infection or cross infection, including, but not limited to, the transmission of infectious diseases from one patient to another. Contamination of the device may lead to injury, illness or death of the patient or end user.

PRECAUTIONS

1. Please read all instructions prior to use.
2. Strict aseptic technique should be followed.
3. The use of this product in patients with compromised hepatic function should be carefully considered since Rifampin can cause additional stress to hepatic metabolism. Rifampin given at systemic therapeutic doses over multiple days, has been shown to produce liver dysfunction. Fatalities associated with jaundice have occurred in patients with liver disease and in patients taking Rifampin with other hepatotoxic agents systemically. Patients with impaired liver function should be given Rifampin systemically only in
cases of necessity and then with caution and under strict medical supervision. In these patients, careful monitoring of liver function, especially SGPT/ALT and SGOT/AST should be performed prior to therapy.
4. Do not alter practice of pre-, peri-, or postoperative administration of local or systemic antibiotics.
5. U. S. federal law restricts this device to sale by or on the order of a physician.
6. Only physicians qualified in the appropriate surgical techniques should use this surgical graft.
7. The surgeon should thoroughly understand the surgical procedure and the performance characteristics of the surgical graft.
8. Place device in maximum possible contact with healthy, well-vascularized tissue to promote cell ingrowth and tissue remodeling.
9. When unable to close skin over the XENMATRIX™ AB Surgical Graft, ensure that the implant remains moist. Avoid drying of the implant through "continued suction devices" as this may negatively impact the performance of the implant.
10. Due to the orange color in the coating, hydration solution and fluid from surgical drains may be tinted orange..

ADVERSE REACTIONS

Potential complications with the use of any prosthesis may include, but are not limited to, allergic reaction or hypersensitivity to device materials or antimicrobial coating, seroma, infection, inflammation, adhesion, fistula formation, erosion, hematoma, and recurrence of tissue defect.

INSTRUCTIONS FOR USE

Use sterile gloves and/or atraumatic instruments to open package.

Preparation

XENMATRIX™ AB Surgical Graft requires hydration. Some larger graft sizes are supplied with hydration trays.
If the graft is not supplied with a hydration tray, use a sterile medical basin large enough to fully submerge the graft in hydration fluid. Place the entire graft in room temperature sterile saline or sterile water for at least 5 minutes prior to implantation. The safety and effectiveness of hydrating the graft in combination with solutions other than sterile saline or sterile water have not been tested.

⚠ **Warning:** Do not hydrate the graft for more than 20 minutes. The antimicrobial surface coating has been optimized for hydration times less than 20 minutes. Hydrating for longer than 20 minutes may impact the function of the antimicrobial coating of the implant.

Sizing

Using the proper graft size is essential. The surgical graft should be large enough to provide sufficient overlap beyond the margins of the defect on all sides. Using a XENMATRIX™ AB Surgical Graft that is too small for the defect can cause excessive tension on the suture line.

Deployment

XENMATRIX™ AB Surgical Graft may inhibit deployment through trocars during laparoscopic repairs. If the XENMATRIX™ AB Surgical Graft cannot be easily deployed down the trocar, remove the trocar and insert the implant through the incision. Reinsert trocar.

Fixation

Appropriate fixation is essential to ensure secure graft contact with well vascularized tissue. XENMATRIX™ AB Surgical Graft should be fixated with suture under minimal or no tension. Careful attention to fixation placement and spacing will help prevent excessive tension or gap formation between the graft and fascial tissue.

PERFORMANCE DATA

The safety and performance of the XENMATRIX™ AB Surgical Graft was evaluated in the following assessments::

Biocompatibility testing

Biocompatibility testing in accordance to the current ISO 10993 series was conducted on the finished device and the results indicate that the device is biocompatible per these standards.

Bench testing

Bench testing was conducted comparing the XENMATRIX™ AB device with currently marketed surgical mesh. The testing included the following:

1. Physical Characteristics:
   a. Device Thickness
   b. Device (Flexural) Stiffness
2. Functional Characteristics:
   a. Burst Strength
   b. Suture Pullout Strength c. Tear Resistance

Results demonstrate that the physical and functional characteristics of XENMATRIX™ AB Surgical Mesh are comparable to those of currently marketed surgical mesh devices.

In vivo strength determinations

The device was implanted in a 28 day, porcine evaluation model and tested for strength characteristics in comparison to currently marketed surgical mesh. This study assessed the following characteristics of the implanted mesh at Time zero (T_0) and Day 28 (D_{28}):

1. Mechanical Testing
   a. Tensile Strength Testing
   b. Tissue Ingrowth Testing
   c. Device Burst Testing
2. Percent Area Contracture
3. Peritoneal Tissue Attachments
4. Histology

Results demonstrate that the in vivo performance of XENMATRIX™ AB Surgical Mesh is comparable to those of currently marketed surgical mesh devices.

Drug Content and Impurities of the Antimicrobial Agents Rifampin and Minocycline

Analytical and in vitro testing was also performed on the device and included speed to kill, kinetic drug release (KDR), drug content and impurity, and polymer degradation testing. The test results demonstrated comparable performance to currently marketed surgical mesh devices with respect to these parameters.

Animal Testing

An in vivo porcine implantation study was performed to investigate the device's mechanical strength and the host inflammatory response to the device over a 28 day duration. At 28 days, the XENMATRIX™ AB surgical mesh had greater tissue-ingrowth/T-Peel Force values than the control surgical mesh. The mechanical strength values (i.e., Ultimate Load/Burst Force, Peak Tensile Strength) of the graft alone were lower than the control surgical mesh.

In addition, two in vivo dorsal implant rabbit infection model studies were performed. Devices were inoculated with bacteria at implantation, and at 7 days, post-implantation, bacterial colonization quantifications were conducted. At that time point the antimicrobial coating on the XENMATRIX™ AB was observed to prevent bacterial colonization of the device in comparison to a control surgical mesh.

The relevance of these studies to human clinical performance outcomes has not been demonstrated.

The correlation of these studies has not been demonstrated to be predictive of positive human clinical outcomes.

Human clinical data

None.

The claim of reduction of colonization has not been established with human clinical data, nor has a clinical impact associated with this claim been demonstrated.

PATIENT RECORD LABEL

A patient record label that identifies the type, size, and lot number of the implant is attached to every package. The label should be incorporated into the patient's permanent medical record to clearly identify the device that was implanted. If you experience a product failure, please contact Davol, Inc. at 1-800-556-6275 for instructions on returning the product.

	Contents		Upper Limit of Storage Temperature
	Do not use if package is damaged.	Rx	U. S. federal law restricts this device to sale by or on the order of a physician only