Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Rosen et al. Randomized Controlled Trial Comparing Biologic versus Synthetic Mesh for the Single Stage Repair of Contaminated Ventral Hernias.

Submitted to JAMA Surgery.

This supplement contains the following items:

1. Original protocol, final protocol with amendments and summary of changes.
2. Original statistical analysis plan (protocol description), final statistical analysis plan, summary of changes

Executive Summary of Protocol

Study Synopsis

Title: Multicenter, prospective randomized trial comparing biologic versus synthetic mesh for the repair of contaminated ventral hernias

Investigational Product

Soft Mesh, Bard Davol
Strattice Mesh, Lifecell

Protocol Number

NCT#02451176
IDE# G120130

Study Design

Multicenter, parallel group, randomized controlled trial

Number of Sites

Up to 5 academic medical centers with specialized abdominal wall reconstruction units

Number of Subjects

253 contaminated ventral hernias

Study Population

Male and female patients at least 21 years of age presenting with a clean-contaminated or contaminated ventral hernia for planned single stage repair

Study Treatment

Medium weight polypropylene mesh or non-crosslinked porcine dermis mesh placed in the retromuscular position during complex abdominal wall reconstruction

Study Objective

To determine the safety and efficacy of synthetic mesh as compared to biologic mesh for the single staged repairs of contaminated ventral hernias

Study Endpoints

Primary Outcome

1. Efficacy- Incidence of hernia recurrence at 2 years following hernia repair.
2. Safety-Incidence of surgical site occurrence requiring a procedural intervention (SSOPI) throughout the study period.

Secondary Outcome

1. Incidence of postoperative adverse events at 30 days postoperatively measured by overall adverse event rate, Clavien Dindo Grades I-V, and Comprehensive Complications Index
2. Hernia related quality of life at baseline, 1m, 6m,12m, and 24 m as measured by HerQles abdominal wall function score
3. Overall quality of life at baseline, 1m, 6m,12m, and 24 m as measured by EQ5D summary score and VAS score
4. Cost of abdominal wall reconstruction of contaminated defects as measured by direct cost, 30 day costs and prosthetic cost.

Clinic Visits

Baseline, surgical admission, 30 days, 6 months, 12 months, and 24 months

Study Criteria

Inclusion Criteria

1. age $\geq$21
2. hernia defects $\geq$9 cm^2
3. contaminated wound class (CDC II or III)
4. elective single-staged repair
5. intraoperative achievement of fascial closure
6. willing candidates to receive either polypropylene or a biologic prosthesis.

Exclusion Criteria

1. CDC wound class I or IV
2. BMI >45 kg/m^2
3. chronic immunosuppression (>10 mg of prednisone/day)
4. collagen vascular disorder
5. severe malnutrition (albumin <2.0 g/dL)
6. ascites refractory to medical management
7. end stage renal disease (on hemodialysis)
8. liver disease (hepatitis B and C or total bilirubin >3.0 mg/dL)
9. smoking within1 month of surgery
10. pregnancy
11. undergoing minimally invasive repair
12. active mesh infection. Mesh infection is defined as synthetic mesh that is not incorporated, exposed, or has chronic draining sinus with pus around the material.

	Screening Visit	**Pre-Definitive Closure**	**Day of Definitive Closure**	**Follow Up**	
	≤ 45 days prior to Definitive Closure			4 Weeks	
Inclusion/Exclusion	x	x			
Informed Consent	x	x			
Medical History	x				
Physical Exam	x		x		
CBC	x				
Comp Metabolic panel	x				
Albumin	x				
prealbumin	x				
HbA1`C	x				
Urinalysis	x				
CT-Abdomen Pelvis	x				
Pre-op Standard of care	x	x	x		
Randomization			x		
Placement of Study Mesh/Investigator Fee			x		
Assessment of Repair Failure or Hernia Recurrence				x	
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Adverse Event Assessment	x			x	

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1. Objectives

The primary objective of this study is to determine the safety and efficacy of synthetic versus biologic mesh in the repair of clean contaminated and contaminated ventral hernias.

The specific aims of the proposal are:

1. To demonstrate that a single-stage repair of clean-contaminated (Class 2) or contaminated (Class 3) ventral hernias using a macroporous light-weight polypropylene synthetic mesh will result in superior clinical outcomes compared to a biologic mesh.
    a. Task 1- Demonstrate that repairs of clean-contaminated and contaminated ventral hernias performed with macroporous light-weight polypropylene mesh will result in fewer recurrent hernias and fewer surgical site occurrences requiring procedural intervention at 24 postoperative months compared to repairs of clean-contaminated and contaminated ventral hernias performed with biologic mesh.
    b. Task 2- Compare postoperative pain, and demonstrate greater change in preoperative to postoperative quality of life (QOL) at 1 month, 6 months, 12 months, and 24 months following clean-contaminated or contaminated ventral hernia repair with a macroporous light-weight polypropylene mesh versus a biologic prosthesis.
2. To demonstrate that a macroporous light-weight polypropylene mesh is the more cost-effective strategy than a biologic prosthetic in clean-contaminated and contaminated abdominal wall reconstruction.
    a. Task 1-Estimate direct and indirect economic costs associated with clean-contaminated or contaminated ventral hernia repair using either polypropylene mesh or biologic mesh from a limited societal perspective.

b. Task 2 – Perform health utility valuation in patients undergoing repair of clean-contaminated or contaminated ventral hernias using either polypropylene mesh or biologic mesh.
c. Task 3 – Calculate and compare incremental cost-effectiveness ratios for patients undergoing repair of clean-contaminated or contaminated ventral hernias using polypropylene mesh versus biologic mesh.

2. Background and Rationale

Ventral hernia (VH) is a frequent sequela of abdominal surgery, occurring after up to 10-20% of laparotomy incisions.[1, 2] This results in almost 250,000 annual ventral hernia repairs in the United States, making it one of the most common procedures performed by general surgeons.[3] The annual health care expenditures associated with hernia repairs now exceeds $5 billion US dollars. [4] Since prosthetic mesh has been shown to reduce recurrence rates by over 50%, most surgeons agree that some form of prosthetic reinforcement should be added to all but the smallest ventral hernia repairs.[5] Traditionally, this has involved a permanent prosthetic material in clean cases (without bacterial contamination) at relatively low cost (approximately $150 for a 900$cm^2$ mesh). The management of more complex hernias where infection or contamination is present is not well defined. These patients are often severely disabled by the chronic infectious nidus and suffer a very poor quality of life until reconstruction of their abdominal wall anatomy and resolution of the infection. Historically, this has involved a two-stage approach for hernias where simultaneous gastrointestinal, biliary, and/or genitourinary procedures were performed or if there was an active infection of a prosthetic material. The first stage involved removing the infectious or contaminated source and performing

a temporary closure of the abdominal wall with an absorbable material. This approach of so-called “planned hernia” would almost uniformly require another major operation.

Approximately 6 months to one year later, the abdominal wall is repaired with a permanent synthetic material in a clean setting. This approach avoids placing the synthetic mesh in the field of contamination but is associated with significant morbidity as it requires two operations and potential long-term disability during the recovery period. Recognizing the limitations of this two-stage approach, new biologic materials have been designed to offer a single-stage approach for infected and contaminated abdominal wall reconstruction. These materials are derived from various sources including human or porcine dermis, bovine pericardium, or intestinal submucosa. They are processed in such a way as to render an acelluar collagen-rich graft that reportedly acts as a cellular scaffold to allow native tissue in-growth and regeneration of tissue. They are marketed as resistant to infection and therefore as a suitable hernia repair material for clean-contaminated and contaminated abdominal wall defects. However, these products are very expensive with a 400cm^2 porcine dermal graft costing over $10,000, and currently represent the most rapidly growing market in hernia repair, with estimates of almost $500 million dollars in annual revenue by the year 2013.[6] Despite the rapid acceptance of these materials, there is little preclinical or clinical evidence to support their claims of regeneration, or that they provide a durable repair to the abdominal wall in the setting of a clean-contaminated (Class 2) or a contaminated (Class 3) surgical procedure.

In our experience, the single-stage repair of contaminated abdominal wall defects with these biologic grafts has resulted in a 40%-80% recurrence rate with long term follow up.[7, 8] Given these disappointing results, other investigators have evaluated the role of synthetic mesh in the repair of contaminated abdominal wall defects in small, retrospective non-randomized trials.[9-11] Importantly, several recent modifications to

polypropylene mesh have yielded potential options for repairing contaminated defects. These modifications include reducing mesh weight, increasing mesh porosity, and utilizing monofilament unwoven material that resists bacterial colonization in animal studies.[12, 13] In fact, our lab has recently evaluated 9 commercially-available prosthetic materials and has found that certain meshes can clear bacterial contamination similar to biologic grafts in a rat hernia model. These materials have been used for years in clean repairs of large complex abdominal wall defects with significantly lower recurrence rates (<5%) than a biologic mesh.[14] Beyond doubt, a non-biased prospective randomized trial is long overdue to compare the safety and efficacy of a biologic graft versus a macroporous light-weight polypropylene synthetic material for the repair of complex ventral hernias. This study will compare the safety, efficacy, and cost-effectiveness of a permanent synthetic mesh versus a biologic prosthesis for the open repair of ventral hernias in the setting of clean-contaminated (Class 2) or contaminated (Class 3) surgical procedures.

This study will have a major impact on the field of hernia surgery, as the study findings will provide an objective guide to mesh selection, optimize surgical approaches for complex ventral hernia repair, and ultimately significantly improve patient outcomes. The lack of data as to the ideal mesh selection for complex ventral hernia repair has resulted in physicians relying on anecdotal experience, industry marketing, and personal bias. Presently, hundreds of thousands of patients are affected by this condition and would significantly benefit from clear practice guidelines regarding the best approach and the most appropriate prosthetic selection for repairing these complex ventral hernias. In order to address this important need, the overall safety, efficacy, and cost-effectiveness of a biologic prosthetic as compared to a synthetic material for the open repair of complex defects should be subjected to a prospective randomized clinical trial.

We hypothesize that reinforcement of single-stage open repairs of complex abdominal wall defects with a macroporous light-weight polypropylene synthetic mesh will result in significantly lower rates of hernia recurrence (HR) and surgical site occurrences requiring procedural intervention (SSOPI) at 24 postoperative months, and greater cost-effectiveness compared to reinforcement with a biologic mesh. We further hypothesize that reinforcement with macroporous light-weight polypropylene synthetic mesh will be associated with a significantly greater change in preoperative to postoperative patient-reported quality of life (QOL) compared to reinforcement with biologic mesh for clean-contaminated or contaminated ventral hernias.

3. Experimental Plan

a. Study Design

We propose a multi-center parallel group, prospective randomized controlled trial comparing 253 patients with clean-contaminated (Class 2) or contaminated (Class 3) abdominal wall ventral hernias undergoing single-stage open repair. Patients will be recruited from surgical clinics at one of 5 major abdominal wall reconstruction units. After completing all screening and baseline procedures subjects will be randomized in a 1:1 fashion to receive either Soft Mesh™ by CR Bard™, a macroporous monofilament polypropylene permanent mesh, or Strattice™ mesh by LifeCell™, a non-crosslinked porcine dermal biologic graft, for the single-stage open reconstruction of clean-contaminated and contaminated abdominal wall defects. The primary outcome variables will be the absence of surgical site occurrence requiring procedural intervention and the absence of a hernia recurrence from the time of surgery up to 24 months of postoperative follow-up.

b. Number of Centers

Patient recruitment and surgical procedures will be performed at one of 5 academic medical centers with dedicated abdominal wall reconstruction units. Patients will be recruited directly from the respective medical center's surgery clinics.

c. Number of Subjects

A total of 253 subjects will be randomized 1:1 to receive either a synthetic or biologic mesh for the single stage treatment of a contaminated ventral hernia.

d. Study Duration

It is estimated that this trial will take 2-4 years to accrue all the surgical patients and another 2 years to complete long term follow up.

4. Subject Eligibility

Investigators will maintain a screening log that includes all patients that were consented for the trial and reasons for ineligibility or refusal to participate.

a. Inclusion Criteria

Patients will be included in this study if they are 21 years of age or older (including women of childbearing age), undergoing a planned single-stage open reconstruction of a contaminated (CDC wound class 2 or 3) (Appendix 3) abdominal wall defect (including concomitant procedures: creation of a stoma, bowel resection, panniculectomy, removing uninfected mesh, and gastrointestinal, genitourinary, or gynecologic procedure) under general anesthesia, can achieve midline fascial closure, and have a parastomal hernia or midline defect at least 9 cm^2.

b. Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria: are undergoing a laparoscopic or robotic repair of the abdominal wall defect, have a CDC class 1 or 4 wound (see CDC guidelines below),have a defect that the surgeon cannot achieve primary fascial apposition and requires a bridge of mesh, body mass

index (BMI) >45 kg/m^2, chronic immunosuppression including medically-induced with >10 mg of prednisone/day, collagen vascular disorder, severe malnourishment (albumin <2.0 g/dl), ascites refractory to medical management, end stage renal disease (indwelling hemodialysis or peritoneal dialysis), pre-existing liver disease (hepatitis B or C or total bilirubin >3.0 mg/dl), smoking history within 1 month of surgery, current pregnancy, require removal of a prior surgical mesh during a planned ventral hernia repair due to active mesh infection (as defined by a synthetic mesh that is not incorporated into the tissue, is extracorporeally exposed, or has a chronic draining sinus with clear fluid around the material; but not including synthetic mesh that is incorporated into the abdominal wall and not infected), are unable to undergo successful retro-rectus preperitoneal mesh placement, if they object to the implantation of porcine products, or if they are participating in other clinical trials.

5. Subject Enrollment

Patients will participate if they have a clean contaminated or contaminated wound and can undergo a single staged ventral hernia repair. If patients are deemed eligible, they will be consented and randomized to receive either a synthetic or biologic mesh at the time of ventral hernia repair. Subjects, or their legally acceptable representatives, must personally sign and date the consent form before the commencement of any screening procedure.

a. Subject Registration

i. After completion of informed consent, (Appendix 6) each subject will be registered into a RedCap database. All entries will be performed at one of the 5 sites performing the procedures. Subsequent follow up data will be completed by entering into local electronic medical record and completing appropriate clinical report forms, adverse

event forms and any other outcomes required. In addition, the subject's initials, OR date and site location will be entered.

ii. The computer-generated randomization code will be generated for each subject. The first two digits will assign the site number, and the subsequent numbers will be the unique patient identifier.

b. Randomization and Treatment Assignment

i. Eligible patients will be randomized 1:1 in the operating room to undergo open retromuscular incisional hernia repair with either biologic or synthetic mesh after closure of the posterior sheath and just prior to mesh deployment. Randomization will be stratified by medical center, and CDC wound class (clean-contaminated or contaminated) and occurred through a central concealed randomization scheme housed in RedCap by using a random number of blocks with a 1:1 ratio of assigning patients to each arm. The investigator will be blinded to patient randomization assignment until the point of intra-operative device placement whereas patients will remain blinded to patient randomization until the conclusion of the study period.

c. Screen Failures

i. Registered subjects who are ineligible for the study based on screening assessments will be considered screen failures and registered as such with the reason for failure.

6. Treatment Procedures

a. Surgical Procedure

Patients undergoing open ventral hernia repair for clean-contaminated and contaminated abdominal wall hernias meeting inclusion criteria will be

randomized to receive a synthetic mesh or a biologic mesh. Randomization will be carried out using computer-generated randomization blocks at the time of enrollment. Stratified randomized will be used with the strata formulated by medical center then by clean-contaminated or contaminated surgical site class. The Investigator will be blinded to patient randomization assignment until the point of intra-operative device use following final CDC wound classification, whereas patients will remain blinded to patient randomization until the conclusion of the study period. Patients randomized to synthetic mesh will receive Soft Mesh™ (CR Bard™, Murray Hill, NJ), and those patients randomized to biologic mesh will receive Strattice™ (LifeCell™, Branchburg NJ). The use of biologic and synthetic meshes in clean-contaminated and contaminated fields is considered experimental; however, the selection of these prosthetics was based on a careful review of the multiple animal models, preclinical data, and our own clinical experience with each of these materials placed in both clean and contaminated abdominal wall reconstructions.[15-21]

b. Mesh Properties

a. Soft Mesh™ is a medium-weight (44 g/m^2) monofilament macroporous polypropylene synthetic mesh. It does not have an anti-adhesive barrier and must be place in an extraperitoneal position. Our lab has evaluated this material in a chronic rat infection model and has shown clearance rates of bacterial contamination comparable to biologic grafts (Figure 1). This prosthetic has become our material of choice for routine abdominal wall reconstruction and ventral hernia repairs, given its chemical and structural properties. In addition, we have also utilized Soft Mesh™ in the

retrorectus position in several cases of elective bowel surgery, parastomal hernia repair, and inadvertent enterotomies with excellent results including no mesh infections and no long-term hernia recurrences. Other authors have reported excellent outcomes with polypropylene-based synthetic material placed in the extraperitoneal position.[14] Interestingly, reports of placing several forms of polypropylene-based meshes with anti-adhesive barrier coatings into the peritoneal cavity for elective hernia repair with concomitant bowel surgery has shown very high rates of mesh sepsis and subsequent mesh excision.[22] Mesh placed in the intraperitoneal position comes in contact with the viscera and therefore requires some form of an anti-adhesive barrier. We noted that these anti-adhesive barriers prevent bacterial clearance in an experimental study (Figure 1). Based on our findings, it is likely that both the specific type of synthetic mesh and the compartment of the abdominal wall in which it is placed will have significant effects on bacterial clearance and success when placed in a clean-contaminated or contaminated field. Potential extraperitoneal compartments for mesh deployment include the onlay (placed above the fascia in the subcutaneous space) or a retro-rectus (below the muscles but above the peritoneum) position. The onlay position can result in early mesh exposure if wound infection or breakdown occurs and has been shown in other prospective randomized trials to result in a high rate of mesh infections.[23] Alternatively, the retro-rectus repair with synthetic mesh reinforcement has been demonstrated by multiple authors as a durable repair with very low rates of mesh infection and hernia recurrence.[14, 24] For these reasons, we feel it is particularly important to design this

experiment to use an unprotected macroporous medium-weight polypropylene mesh placed in the retro-rectus position.

b. The Strattice™ biologic mesh is derived from porcine dermis and processed to remove the cells but maximally preserve the dermal matrix. The processing avoids the use of collagen cross linking agents in a reported effort to minimize immunogenic response, improve biocompatibility, and ultimately promote rapid revascularization and tissue regeneration.[25] Multiple biologic grafts have been developed to repair contaminated abdominal wall defects, however little comparative data exists to definitively guide selection of these grafts. Our lab has performed several preclinical evaluations of these materials and has chosen Strattice™ based on our findings. Strattice™ mesh showed excellent biocompatibility from an immunologic perspective when compared to other human and porcine derived biologic products.[26] This selection should limit the potential for immunologic responses to the biologic material confounding our results. We also evaluated the ability of various biologic grafts to clear bacterial contamination in a chronic infection rodent model.[27] Strattice™ mesh had the highest rates of bacterial clearance when compared to other porcine derived materials. Interestingly, it appears that based on our findings, Soft Mesh™ and Strattice™ result in similar rates of bacterial clearance, which is the primary driving force of our renewed interest in evaluating the usage of these inexpensive synthetic meshes in clean-contaminated and contaminated fields.

7. Study Procedures

a. Assessment

All patients will undergo our standard pre-operative evaluation and data entered into the case report forms (Appendix 7). Briefly, it will include a complete set of laboratory studies including complete blood count, comprehensive metabolic panel, albumin, prealbumin, HbA1C (for diabetic patients), and urinalysis. Pregnancy test will be performed for those patients of child bearing potential. Photos may be taken of the anterior abdominal wall. An abdominal pelvic CT scan will be obtained preoperatively in all patients based on our standard approach, (abdominal pelvic CT scan within the past twelve months is sufficient) and any issues postoperatively (including suspected recurrence) will be evaluated with a CT scan or other radiologic imaging as clinically indicated. Preoperative demographics and clinical data including sex, race, age, body mass index (BMI), location of the hernia, length and width of the hernia defect, wound classification(per CDC guidelines, table 1), smoking status (active within 3 month of surgery), medical history, surgical history of prior abdominal surgical procedures and prior ventral/incisional hernia repairs will be documented. Intraoperative details will include patient ASA score, patient temperature, use of epidural catheters, size of fascial defect (measured as maximal width and length), fascial layers released (external oblique, posterior rectus sheath, or transversus abdominis muscle), adhesions, concomitant procedures, wound characterization, mesh type, mesh placement, operative time, estimated blood loss, blood transfusion requirement, perioperative antibiotic administration (including type, dose, frequency, and times of initiation and discontinuation), and intraoperative fluid administration. Postoperatively, patients will be evaluated for signs and symptoms of complications along with presence or absence of surgical site infections (SSIs) per CDC

definitions as categorized below, presence or absence of surgical site occurrences (SSOs) and any procedural interventions required to treat these SSOs, presence or absence of hernia recurrence and any reoperations, length of hospital stay, discharge date, time to return of bowel function and any readmission. Wound erythema treated with antibiotics will be considered a wound cellulitis. Wounds that are opened and cultured will be appropriately categorized as postoperative SSIs based on CDC definitions (Appendix 4). Type, dose, frequency, and duration of antibiotics will be recorded. Patients will also fill out HerQLes (Appendix 1) and EQ-5D (Appendix 2) quality of life tools preoperatively and during each post-operative visit, at 4 weeks (± 2 weeks), 6 months (±2 months), 12 months (± 3 months), and 24 months (± 4 months). There is substantial evidence that the majority of hernia recurrences occur within the first 24 months after repair.[5, 28, 29]

Preoperative antibiotic usage will be standardized (as per SCIP protocol) as follows. All patients will receive a second generation cephalosporin within 60 minutes prior to the surgical incisions. Patients with a prior history of penicillin allergy or MRSA wound/mesh infections will instead receive a preoperative dose of intravenous vancomycin. The exact drug, along with the dose, frequency, and time administered will be recorded. All antibiotics will be discontinued after 24 hours of surgery unless otherwise indicated. Prolonged antibiotic usage will be clearly documented as to indication, type, dose, frequency, and duration.

The surgical approach to repairing these defects will be standardized, as previously described. All patients will receive a chlorhexidine skin preparation, an iodine-impregnated skin barrier, and all stoma sites will be over sewn at the muco-cutaneous junction to limit bacterial contamination prior to skin preparation. If patients

have an allergy to chlorhexidine, then Duraprep™ will be utilized. For any patient who has an allergy to iodine, then a Steri-Drape may be used as a skin barrier. Hair will be removed at the time of surgery with electric clippers. The midline fascia will be opened and complete adhesiolysis performed to free up the entire abdominal wall. All concomitant procedures will be performed prior to beginning the abdominal wall reconstructive phase and documented. Intraoperative concomitant procedures will be allowed unless they change the wound classification to a class 4. Acceptable concomitant procedures include: the creation of a stoma, bowel resection, gastrointestinal surgery, genitourinary surgery, gynecological surgery, panniculectomy, and removing uninfected mesh. The abdominal wall is reconstructed by initially incising the posterior rectus sheath just lateral to the linea alba. The release is performed at least 5 centimeters above and below the fascial defect. The posterior rectus sheath is then separated off the rectus muscle to the linea semilunaris. If additional release is necessary to achieve fascial closure, the transversus abdominis muscle or the external oblique muscle may be released at the discretion of the surgeon and documented. The posterior components are then reapproximated to exclude the abdominal viscera from the mesh. If the mesh cannot be placed in the retro-rectus or preperitoneal position, then the patient will be excluded from the study. Unless contraindicated due to drug allergies, a pulse lavage antibiotic irrigation using a 3 liter bag with Gentamycin (240 mg), Ancef (3gm), and Bacitracin (50,000 units) will be applied to the posterior rectus sheath and subcutaneous tissues after the components are reapproximated and prior to mesh placement. If there is a drug allergy, then pulse lavage irrigation with sterile saline only will be applied. Final wound classification will occur just prior to mesh placement per CDC criteria. Surgical wounds will be classified based on CDC criteria and only Class 2 and 3 wounds will be included in this study:

Class 2: Clean-Contaminated

Operative wounds in which the respiratory, alimentary, genital*, or urinary tract 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.

*Includes female and male reproductive tracts

Class 3- Contaminated

A surgical field with any of the following: open, fresh, accidental wounds; operations with major breaks in sterile technique or gross spillage from the gastrointestinal tract; and incisions in which acute, nonpurulent inflammation is encountered.

Following wound classification, the allocation of the patient to either the biologic mesh cohort or the permanent synthetic mesh cohort will be revealed to the operating surgeon, according to the previously-described computer-generated block randomization scheme stratified by wound classification and medical center. The corresponding prosthetic material will then be placed with at least 5 cm of fascial coverage on all sides of the defect. The mesh will be fixated with trans-abdominal #1 Maxon or PDS sutures at 5-10 cm intervals. Number of sutures to secure the mesh will be documented. All patients will have closed suction drains placed above the mesh and below the fascial closure. These drains will be removed postoperatively when the collected fluid is < 30 cc/day for 48 hours and documented. The fascia will be closed with a running or interrupted Maxon or PDS #1 suture. The skin will be closed loosely with staples. Dry sterile

dressings will be placed at the conclusion of the procedure and will be removed on postoperative day 2. No further dressings will be applied to the wound.

b. Follow up Phase

Patients will be evaluated in the surgeon's clinic at prespecified post-operative time points. Patients will receive a clinical exam, CRFs completed, patient reported outcomes will be completed and radiologic imaging will be performed if a recurrence is suspected. These time points will occur at 1 (±15 days), 6 (±2 months), 12 (±2 months), and 24 (±4 months) months after surgery or additionally if complications occurred.

c. Definition of Endpoints

Postoperative complications will be defined and recorded on the CRF's based on CDC standardized terms and definitions for Surgical Site Infections as follow: [30, 31]-See appendix 4.

Superficial Incisional Surgical Site infection (SSI)

A **superficial incisional SSI** must meet the following criteria:

Infection occurs within 30 days after the operative procedure AND involves only skin and subcutaneous tissue of the incision AND patient has at least ONE of the following:

a. purulent drainage from the superficial incision.

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 and is culture-positive or not cultured AND the patient has at least one of the following signs or symptoms: pain or tenderness, localized swelling, redness, or heat. A culture-negative finding does not meet this criterion.

d. diagnosis of superficial incisional SSI by the surgeon or attending physician.

NOTE:

a. Do NOT report stitch abscess (minimal inflammation and discharge confined to suture penetration site) as an infection.

b. Do NOT report a localized stab wound or pin site infection. Instead, report these as skin or soft tissue infections, depending on their depth.

c. “Cellulitis" by itself does NOT meet criteria for superficial incisional SSI

d. If infection involves or extends into the fascial and muscle layers report as a deep incisional SSI.

Deep Incisional SSI

A **deep incisional SSI** must meet the following criteria:

Infection occurs within 30 or 90 days after the operative procedure AND the infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision AND patient has at least ONE of the following:

a. purulent drainage from the deep incision but not from the organ/space component of the surgical site

b. a deep incision spontaneously dehisces or is deliberately opened by a surgeon AND is culture-positive or not cultured AND the patient has at least one of the following signs or symptoms: fever (>38°C), or 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 is found on direct examination, during invasive procedure, or by histopathologic examination or imaging test.

d. diagnosis of a deep incisional SSI by a surgeon or attending physician.

NOTE:

a. Classify an infection that involves both superficial and deep incision sites as a deep incisional SSI.
b. Classify infection that involves superficial incisional, deep incisional, and organ/space sites as deep incisional SSI. This is considered a complication of the incision.

Organ/Space SSI

An **organ/space SSI** must meet the following criteria:

Infection occurs within 30 or 90 days after the operative procedure AND infection involves any part of the body, excluding the skin incision, fascia, or muscle layers that is opened or manipulated during the operative procedure AND the patient has at least ONE of the following:

a. purulent drainage from a drain that is placed into the organ/space

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 found on direct examination, during invasive procedure, or by histopathologic examination or imaging test.

d. diagnosis of an organ/space SSI by a surgeon or attending physician and meets at least one criterion for a specific organ/space infection site listed in NHSN.

All study co-investigators agree to follow these CDC definitions of SSIs for study subjects enrolled in this trial to maximize objectivity of this study measure.

Surgical Site Occurrence

A surgical site occurrence (SSO) will be defined as a complication or adverse event occurring at the surgical site, including but not limited to, superficial, deep incisional, and organ/space surgical site infections. Consensus definitions and treatment plans for common SSOs following open complex ventral hernia repair were developed *a priori* by the co-investigators for the purposes of this study protocol (Appendix 6). All study co-investigators agree to follow these consensus definitions and treatment plans for study subjects enrolled in this trial to maximize objectivity of this outcome measure.

Surgical Site Occurrences Requiring Procedural Intervention

A surgical site occurrence requiring procedural intervention (SSOPI) will be defined as a complication or adverse event occurring at a surgical site that is managed or treated with an invasive procedure. Consensus definitions and treatment plans for common SSOs following open complex ventral hernia repair were developed *a priori* by the co-investigators for the purposes of this study protocol (Appendix 5). All study co-investigators agree to follow these consensus definitions and treatment plans for study subjects enrolled in this trial to maximize objectivity of this study measure.

Ventral Hernia Recurrence

A ventral hernia recurrence (HR) will be defined as any fascial defect of the anterior abdominal wall located within 7 cm of the index ventral hernia repair site detected by physical exam or abdominal computed tomography (CT) examination. These defects will be categorized as to whether they occur at the midline or parastomal hernia site, or both. Alternatively, for patients that are not amenable to come to the hospital for an in-person visit, recurrence will be assessed using a validated patient-reported outcome tool denominated the Ventral Hernia Recurrence Inventory

(VHRI)(Appendix 1).[32] The VHRI is a short 3-question survey that can be applied in person or through a telephone contact, and was shown to have higher sensitivity and specificity to diagnose hernia recurrence than physical examination. Also, it was shown to have the ability to rule out hernia recurrence when patients answer “no” to its questions. Patients that respond yes to any question in the hernia recurrence inventory will be encouraged to present for a clinical and radiographic evaluation. Any patient that reports a bulge and does not have further follow up will be considered to have a recurrence. All radiographic imaging will be reviewed by 3 blinded investigators and consensus (2 of 3) will be considered for confirmation of the repair integrity.

8. Removal of Subjects

A subject has the right to withdraw from the study at any time, for any reason, without prejudice to his or her future medical care by the physician or at the institution. Any subject who withdraws consent to participation in the study will immediately be removed from further treatment and/or study observation on the date of request. The investigator has the right to withdraw a subject from the study if any of the following occurs:

• Refusal by the subject to continue observations

• Decision by the investigator that termination is in the subject’s best medical interest

• Loss to follow-up

Should a subject (or legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable case report forms. A complete final evaluation and assessments should be made at the time of the subject’s withdrawal. The End of Study case report form will be completed with an explanation for the withdrawal. If the withdrawal of a subject is due to an adverse event, follow-up visits should be scheduled until the adverse event has resolved or stabilized. Unless consent has been withdrawn, follow-up

data on deaths and hospitalizations will be collected until study termination. However, unless specifically requested by the patient, the patient will be followed for the primary endpoint until end of study.

a. Lost to follow up

A patient will be considered lost to follow up after at least 6 attempts at contact via telephone, email and mailing of the patient reported outcomes forms with a 10 dollar incentive.

9. Adverse Event Reporting

a. Definitions

i. Adverse Events

An adverse event is an undesirable medical occurrence (sign, symptom, or diagnosis) that occurs in a subject after the initiation of the study, whether or not considered to be device related. Elective hospitalizations for pre-existing conditions (ie, any systemic illness or elective surgery) are not adverse events. Abnormal laboratory values should not be reported as adverse events; however, any clinical consequences of such abnormal values should be reported as adverse events.

ii. Serious Adverse Events

A serious adverse event is defined by regulatory agencies as one that suggests a significant hazard or side effect, regardless of the investigator's or sponsor's opinion on its relationship to investigational product. This includes, but may not be limited to, any event that (at any dose):

• is fatal

• is life-threatening (places the subject at immediate risk of death)

• requires in-patient hospitalization or prolongation of existing hospitalization

• is a persistent or significant disability/incapacity

• is a congenital anomaly/birth defect

A hospitalization meeting the regulatory requirement for “serious” criteria is any in-patient hospital admission that includes a minimum of an overnight stay in a health care facility.

Any event that does not exactly meet this definition yet which, in the investigator’s opinion, represents a significant hazard, can be assigned the “other significant hazard” regulatory reporting serious criteria.

Additionally, important medical events that may not be immediately life-threatening or result in death or hospitalization but which may jeopardize a subject or require intervention to prevent one of the outcomes listed above, or result in urgent investigation, may be considered serious.

b. Reporting Procedures for All Adverse Events

All adverse events occurring after randomization observed by the investigator or reported by the subject (whether or not attributed to investigational product), will be reported on the case report form. Medically significant adverse events considered related to the investigational product by the investigator or the sponsor will

be followed until resolved or considered stable. The following attributes must be assigned by the investigator: description; dates of onset and resolution and action taken. The investigator may be asked to provide follow-up information.

All adverse events, serious or not, that result in a subject's permanent withdrawal from the study must be reported in the CRF. The End-of-Study case report form will be completed, giving details of the withdrawal and, if needed, the General Comments case report form will also be completed.

All deaths occurring on study must be reported and cause of death should be investigated. This includes deaths until the termination of the study or a maximum of 48 months since enrollment of the subject, whichever is earlier.

It will be left to an investigator's clinical judgment as to whether or not an adverse event is of sufficient severity to require a subject's removal from treatment.

c. Serious Adverse Event Reporting Procedures

All serious adverse events must be reported in the CRF within 1 working day of discovery or notification of the event. Initial serious adverse event information and all amendments or additions must be recorded on a Serious Adverse Event Report form.

10. Statistical Considerations

a. Study Design

i. Randomized controlled, parallel, single blinded multi-center trial

b. Study Endpoints

i. Primary Endpoints

1. Efficacy- hernia recurrence rate at 2 years' time point.
2. Safety-Rate of Surgical site occurrence requiring a procedural intervention (SSOPI) throughout the study period.

ii. Secondary Endpoints

1. Adverse Events

a. Overall Rates

b. Clavien Dindo Grades I-V

c. Comprehensive Complications Index

2. **Hernia Related Quality of Life-** HERQLES, Change from baseline

3. Overall Quality of Life-EQ5D, Change from baseline

4. Cost

c. Sample Size Considerations

i. We are investigating two primary outcomes: surgical site occurrences requiring procedural intervention (SSOPI) and hernia recurrence (HR). Surgical site occurrences requiring procedural intervention (SSOPI) is a repeated binary outcome measurement. Hernia recurrence (HR) is a single binary outcome measurement. In a multi-institutional retrospective review of clean-contaminated and contaminated ventral hernia repair, hernia recurrence rates were 29.21% versus 7%, and surgical site occurrences requiring

procedural intervention were 39.02% versus 9.01% for the biological mesh and permanent synthetic mesh cohorts, respectively. Based on review of these multi-institutional data, an estimated 253 patients will be enrolled in the proposed trial. Assuming a maximum 20% loss to follow-up, 202 patients will remain in the study sample for a 1:1 randomized allocation to each treatment arm (101 subjects per cohort). At the two-tailed overall (two hypotheses) type I error rate of 0.05, the study will have 92% power to detect a significant difference in the rates of hernia recurrence (29.21% vs. 7%, and a 100% power to detect a significant difference in surgical site occurrences requiring surgical intervention for the primary hypothesis (39.02% vs. 9.01%; with four repeated measurements and autoregressive correlation of rho=0.5) With 4 centers each performing approximately 1 eligible procedures per week, there will be 192 total procedures performed per year, from which it would be feasible to achieve the total enrollment goal of 253 subjects within 2 years.

d. Planned Methods of Analysis

i. General Approach

Continuous data will be described using median values with interquartile ranges (IQR) and comparisons made using Wilcoxon's rank sum test. Categorical data will be described using counts and proportions with comparisons performed using Pearson's chi square or Fisher's exact test.

ii. Analysis of Key Study Endpoints

1. Primary Endpoint

a. **<u>Specific Aim 1</u>** - To demonstrate that a single-stage repair of clean-contaminated (Class 2) or contaminated (Class 3) ventral hernias using a

macroporous light-weight polypropylene synthetic mesh will result in superior clinical outcomes compared to a biologic mesh.

b. **Primary Analyses of Primary Outcomes:** The primary outcomes are rates of surgical site occurrences requiring procedural intervention (SSOPI) and hernia recurrence (HR) assessed postoperatively at 1 month, 6 months, 12 months, and 24 months. For SSOPI with 4 repeated binary measurements, a generalized mixed model analysis with repeated measures will be performed to determine if a significant difference exists between the biologic mesh and the permanent synthetic mesh cohorts in the rate of SSOPI. For HR, which is a single binary outcome, simple chi-square tests will be used for unadjusted analyses and a logistic regression model will be used for adjusted analyses. As this is a randomized trial, differences in baseline demographic and clinical characteristics between the biologic mesh cohort and the permanent synthetic mesh cohort are expected to occur at random. Any significant differences found among the demographic or preoperative clinical characteristics between the two treatment groups will be controlled for in the final analysis to limit potential confounding of results.

c. Secondary Analyses of Primary Outcomes:

These primary outcomes will also be assessed as a time-to-hernia-recurrence. In these analyses, the time-to-recurrence in the synthetic mesh group will be compared to the time-to-recurrence in the biologic mesh group using a two-sided log-rank test. The null hypothesis is that the time-to-recurrence is the same between the two groups (H0: Hazard Ratio = 1), and the alternative hypothesis is that the time-to-recurrence is significantly greater for the permanent synthetic mesh cohort compared to the biologic mesh cohort (H1: Hazard Ratio not= 1). Since this is a randomized clinical trial, observed differences in other covariates between the two study groups are assumed to arise by chance. Therefore, the simple unadjusted analysis is sufficient to answer the research question, assuming adequate power (see above). However, since the association between other covariates and time-to-recurrence may be of interest and because group imbalances may occur due to chance, it is of interest to consider further analyses that adjust for covariates in the relationship of time-to-recurrence and mesh type. To that end, the following multivariable models are pre-specified: 1) Demographics: age, race, gender, and mesh type; and 2) Known linkages to hernia recurrence: BMI, history of smoking, size of defect, number of previous

hernia repairs, and mesh type. These models will be fit with Cox proportional hazards models. If other covariates are found to be highly imbalanced between groups or found to be associated with time-to-recurrence, they can also be included in multivariable models; however, this type of post-hoc model selection is to be considered inferior to the pre-specified models and is speculative in nature. A similar analysis will ensue for the time-to-a-healed-wound outcome. The null hypothesis is that the time-to-a-healed-wound is the same between the two groups (H0: Hazard Ratio = 1), and the alternative hypothesis is that the time-to-a-healed-wound is significantly greater for the permanent synthetic mesh cohort compared to the biologic mesh cohort (H1: Hazard Ratio not= 1).

2. Secondary Endpoint

The secondary outcomes are pain and quality of life (QOL). The assessment of the association between these outcomes and mesh type will parallel what was described above for the primary outcome. The differences are as follows. First, the primary analysis will utilize an ANCOVA model adjusting for baseline pain (QOL) and correlations among repeated measurements. The null hypothesis is that the pain (QOL) is the same, on average, between the synthetic and biologic mesh groups (H0: Beta-mesh-type = 0). The alternative hypothesis is

that the pain (QOL) is different, on average, between the two groups (H1: Beta-mesh-type not= 0). Second, the multivariable modeling will utilize multiple linear regressions. A mixed model analysis with repeated measures will be performed to determine if a significant difference exists between the biologic mesh and the permanent synthetic mesh cohorts in the mean change in score from the preoperative assessment to the postoperative assessments at 1 month, 6 months, 12 months, and 24 months for the EQ-5D and HerQLes quality of life instruments. The null hypothesis is that there is no significant difference between the biologic mesh and the permanent synthetic mesh cohorts in the mean change in score from the preoperative to the postoperative assessments at any of the time points for either the EQ-5D or the HerQLes quality of life instruments. The alternate hypothesis is that there is a significantly greater change in EQ-5D and HerQLes scores from the preoperative assessment to the postoperative assessment at each of the time points for the permanent synthetic mesh cohort compared to the biologic mesh cohort

In these data analyses, we will explore the possibility of medical center effect and treatment by medical center interaction. In particular, in the regression analyses, we will use indicator variables for medical center effect and indicator variable*treatment for possible treatment by medical center interaction. If treatment by medical center interaction is significant, then it is more

appropriate that the treatment effects are summarized by medical center.

Cost analysis: Demonstrate that a macroporous medium-weight polypropylene mesh is the more cost-effective strategy than a biologic prosthetic in clean-contaminated and contaminated abdominal wall reconstruction.

The first task to address this specific aim will be to estimate direct and indirect economic costs associated with clean-contaminated and contaminated open ventral hernia repair. A micro-costing approach will be used assuming a limited societal perspective. Costs associated with the preoperative, operative, and postoperative phases of care will be considered as it pertains to the management of the ventral hernia. In most cases, one to two preoperative clinic visits will be necessary. Final operative costs will be based on each patient's actual inpatient encounter cost obtained from the participating institutions. Postoperative costs will account for routine outpatient visits, costs incurred for complications, and time lost from work due to ventral hernia management. All costs will be reported in U.S. dollars, adjusted for the years in which the data were obtained. Should institutional data not be available for a particular cost, the best available evidence from currently published analyses will be used. The second task for this specific aim is to perform health utility valuation in patients undergoing open repairs of clean-contaminated and contaminated ventral hernias. Patients will be administered the EQ-5D and the HerQLes instruments at one

preoperative visit and postoperatively at scheduled visits at 4 weeks (± 2 weeks), 6 months (±2 month), and 12 months (± 3 months), and 24 months (± 4 months). HerQLes and EQ-5D valuations will be converted to health utility estimates based on published norms from the Agency for Healthcare Research and Quality (AHRQ). Quality-adjusted life years (QALYs) will be calculated based on these health utilities obtained in the postoperative phase. For a given strategy (light-weight macroporous polypropylene mesh or biologic mesh), it is anticipated that health utility variation will be affected more than survival. As such, calculations of QALYs will assume that all patients survive during the 24 month follow-up period, but differ in their health utility valuation.

Cost-Effectiveness Evaluation

Once costs and QALYs have been calculated for each strategy, a decision analysis model will be constructed incorporating these values and the associated outcomes and complications that are thought to have an impact on which strategy is the better choice for patients. One-way and two-way sensitivity analyses will be performed to help determine the degree to which each variable impacts the decision to choose either a light-weight macroporous polypropylene mesh or biologic mesh for repair of clean-contaminated or contaminated ventral hernias. If appropriate, a multi-way probabilistic sensitivity analysis will be performed incorporating the uncertainty associated with known values for certain variables. Costs,

effectiveness (as measured by QALYs), cost-effectiveness ratios, and incremental cost-effectiveness ratios will be calculated to help determine the best strategy for mesh selection based on the results from this study and published data.

e. Study Oversight

i. Data Safety and Monitoring Board (DSMB)

The DSMB is an independent, multidisciplinary group comprised of surgical and statistical representatives. Safety data (adverse events, deep SSI rates, mesh infections, reoperations, and hernia recurrence rates) will be analysed by an independent statistician and will be reviewed on a 50 patient enrolment interval.

The DSMB will be empowered to recommend early termination of the study if there is evidence of harm or benefit based on all measures reviewed.

The complete monitoring plan can be found in Appendix 8.

11. Investigational Product

a. Strattice Mesh

b. Bard Soft Mesh

Compliance

i. Mesh products will be stored and handled in compliance with standard of care processes at the local institution.

ii. Patients randomized to each mesh shall undergo repair with the assigned mesh. Any patient not receiving the allotted mesh will be registered and considered a protocol violation.

12. Regulatory Obligations

a. Informed Consent (see appendix 6)

For each subject, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the principal investigator, surgeon co-investigator, or one of the approved study coordinators must explain orally and in writing the nature, duration, and purpose of the study in such a manner that the subject is aware of the potential risks, inconveniences, or adverse effects that may occur. The subjects will be informed that they may withdraw from the study at any time. Subjects will receive all information that is required by federal regulations.

After a potential study patient is identified, the investigator or the study coordinator listed in this protocol as a person who will obtain consent will be responsible for instituting the informed consent process in a face-to-face manner. Before starting any study procedures, the investigator will discuss the proposed research study in detail with the potential subject during the office visit to discuss treatment options. The subject will be allowed ample time to read and review the informed consent document, and ask questions. The informed consent document will be reviewed with the subject in depth by the participating investigator or designated member of the research team to ensure that the potential participant has a good understanding of the study protocol; what is required of the study participants; the potential risks and benefits of study participation; and his or her rights as a study participant. The investigators will be available by phone or office visit to answer any questions that the participant may have. After consideration, the subject may return if necessary for another visit with

the investigator to discuss the study, ask questions, and sign the informed consent document to participate in this study.

After the subject has read and reviewed the informed consent document and has agreed to participate, he/she will be asked to sign and date the document. The study member obtaining consent will also sign and date the form, and documentation of the informed consent process will be included in the research file (i.e., the person who obtained consent, where and when consent was obtained, and who was present during the process). A copy of the consent form will be given to the subject.

PROVISIONS FOR SUBJECTS FROM VULNERABLE POPULATIONS

The population to be studied includes adults 21 years of age or over, so children are therefore excluded. Decisionally-impaired and cognitively-impaired persons will not be approached to participate in this study as we are seeking subjects who have the capacity to understand and actively consent to the procedure independently. Pregnant women will be excluded from participating in this study.

Staff and employees of the participating sites (Cleveland Clinic, Greenville Health Systems Vanderbilt University Medical Center, and Washington University) are considered vulnerable populations. Staff and employees of any of the participating sites may be eligible to participate in this study. Since subjects may or may not benefit from this study, we do not want to exclude this population. If an employee is a potential candidate for this study, the subject will be informed during the consent process that his/her participation or refusal to will in no way influence grades, employment, or subsequent recommendations. Every effort will be made to prevent coercion during this initial process and throughout study participation. According to

IRB policy, students and house staff cannot be asked to participate in research conducted while under the direct supervision of the investigator, so those subjects will not be enrolled.

In those instances where potential participants cannot read the consent form because they do not speak English, we will work with the IRB to develop a language-appropriate consent form. In addition, a qualified translator will be present to assist with obtaining the informed consent of the participant.

In addition, in the unusual situation where a subject cannot read a consent form due to illiteracy or blindness, a member of the research study staff will read and explain the consent form to the participant or to the participant's legally-authorized representative. A witness, who will sign and date the consent form, must also be present during this oral presentation.

b. Subject Confidentiality

Anonymity and confidentiality of subjects participating in this study will be maintained. The only potential identifiers on any study documents submitted to the sponsor or designee will be subject study numbers, dates of birth, and dates of procedures. Every effort will be made to maintain the confidentiality of documents that identify the subject by name (e.g., signed informed consent documents, clinic charts), except to the extent necessary to allow monitoring by the Center for Clinical Research at Cleveland Clinic, internal monitoring by any of the participating sites, or auditing by the FDA or other regulatory authorities. Should the name and/or address of a subject participating in this trial be on a document submitted to the FDA or other regulatory authority (e.g., laboratory report), the name and/or address will be completely blocked out and replaced with the subject study number.

Additionally, patient charts and clinical records will be requested and reviewed so that protocol adherence and source documentation can be verified. There is a possibility that the Institutional Review Boards of any of the participating sites, the Food and Drug Administration, and possibly foreign regulatory agencies may review the de-identified study records.

All information collected, such as name or medical record number, will be stored utilizing a customized Research Electronic Data Capture (REDCap®) database program for multi-institutional data collection. This is in a secure network/firewall protected electronic database to which only the investigator and the designated members of the study team will have access using an individual assigned login and password. Only approved study members listed on the IRB protocol will have access to the separately-stored master list. User rights will be assigned such that the designated research coordinator at each site may only enter and review data from that site. Only the Principal Investigator, Lead Research Coordinators, and Biostatisticians will be granted access to retrieve patient data from all sites for routine data quality assessments and data analyses. All electronic records pertaining to the clinical study will be password-protected, and only approved study members listed on the IRB protocol will have password access.

Any information about the subject collected on paper, as well as the subject enrollment log linking the subjects to their identifiers, will be kept under lock and key in the Department of Surgery at the corresponding participating site.

13. Administrative and Legal Obligations

a. Study Monitoring

See Appendix 8

b. Alternatives to Participation

The subjects are under no obligation to participate in this study. The subjects may decide not to have mesh used for their hernia repairs. The PI or surgeon co-investigator at each site will discuss all available options. Those subjects not willing to participate in this study may be considered for the alternative treatment of primary defect closure/hernia repair with or without a similar biologic or synthetic product.

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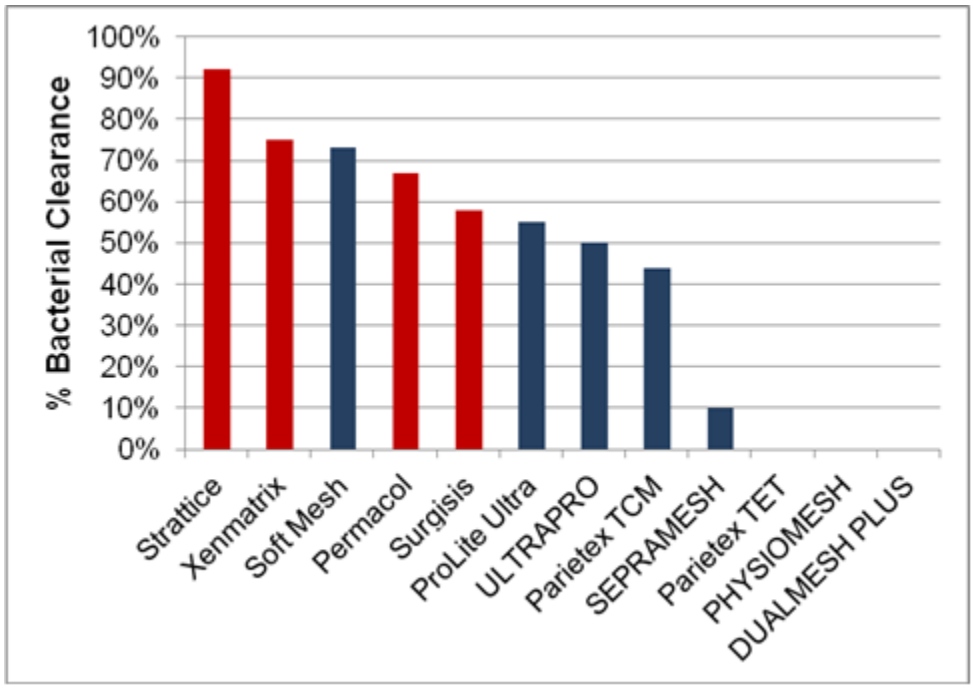
Figure 1:

A rodent model of incisional hernia and chronic infection after exposure to 10'4 colony forming units of MRSA. Bacterial clearance as measured by total resolution of bacterial growth. Strattice versus Soft Mesh p=0.32.



Appendix 1: HerQLes and VHRI Questionnaire

Appendix 2: EQ-5D Quality of Life Tool

Appendix 3: CDC Wound Classification

Appendix 4: CDC Definitions for Surgical Site Infections

Appendix 5: Definitions and Treatment Plans for Surgical Site Occurrences

Appendix 6: Informed Consent

Appendix 7: Complete Case Report Forms

Appendix 8: Study Monitoring Plan

Summary of Significant Protocol Changes

1. PI, Michael Rosen left University Hospitals of Cleveland and joined Cleveland Clinic Foundation during the trial
    a. All patients at UH were attempted to be contacted and reconsented to follow up with Dr. Rosen at CCF.
    b. History of clinicaltrials.gov transfers
        i. Original NCT01746316
            1. Initial release: 11/5/2012
            2. Published 12/7/2012
        ii. Transferred to CCF new NCT0245176
            1. Changed 5/8/2014
2. 5/19/15- Recurrences were further classified by Midline, Parastomal only, or both (midline and parastomal component)
3. 4/23/19-Ventral hernia recurrence inventory questions were added to long term follow up assessments.
4. 9/24/19- As a last effort in the final phase of this study we gained IRB approval to mail study questions with a $10 bill and a SASE to patients who have not completed the 2 year follow-up questions. We will thank them for their participation in the study along with asking them to complete the questions and return to us in the SASE. We have left messages with the patients who have working voice-mails, asking them to return the call to either make an appointment, set up a virtual visit or answer the questions over the phone. Unfortunately, some of the patients do not have an answering machine or a current telephone number listed in EPIC.

Final Statistical Analysis Plan

Any changes to original statistical plan are highlighted in yellow for reference.

1. Baseline Description of Variables

Continuous data were described using median values with interquartile ranges (IQR) and comparisons made using Wilcoxon's rank sum test. Categorical data were described using counts and proportions with comparisons performed using Pearson's chi square or Fisher's exact test.

Tables of summary statistics will be produced by randomized group for a number of baseline variables. The number of missing observations will also be reported.

2. Outcomes

2.1 Primary outcomes

The primary outcomes are rates of surgical site occurrences requiring procedural intervention (SSOPI) and hernia recurrence (HR) assessed postoperatively at 1 month, 6 months, 12 months, and 24 months.

2.2 Secondary outcomes

The secondary outcomes are quality of life (QOL), which includes VAS, EQ5D and HerQles scores. They'll be measured at baseline, 30 days, 6 months, 12 months and 24 months.

Direct costs, 30 day costs, and prosthetic material costs associated with clean-contaminated and contaminated open ventral hernia repair will also be explored.

3. Handling of missing values

When analyzing using the ITT population, model based multiple imputation method will be used to impute missing data at baseline, under the assumption that the missing data has pattern of missing at random. Since the outcomes are repeated measured, the follow up missing will not be imputed but taken care of by mixed effect model.

4. Statistical method

4.1 Statistical procedures for primary outcomes

Primary analysis

For SSOPI with 4 repeated binary measurements, a generalized mixed model analysis with repeated measures will be performed to determine if a significant difference exists between the biologic mesh and the permanent synthetic mesh cohorts in the rate of SSOPI.

For Hernia Recurrence, which is a single binary outcome, simple chi-square tests will be used for unadjusted analyses and a logistic regression model will be used for adjusted analyses. As this is a randomized trial, differences in baseline demographic and clinical characteristics between the biologic mesh cohort and the permanent synthetic mesh cohort are expected to occur at random. Any significant differences found among the demographic or preoperative clinical characteristics between the two treatment groups will be controlled for in the final analysis to limit potential confounding of results.

Prespecified Covariates:

Demographics: age, race, gender, study center, and mesh type

Known linkages to hernia recurrence: BMI, history of smoking, size of defect (hernia width), number of previous hernia repairs, and mesh type.

Post Hoc Additional Covariates:

Given Baseline differences in mesh width and length between the two groups, additional covariates were added to the model. Mesh Width was included.

Secondary analysis

These primary outcomes will also be assessed as time-to-hernia-recurrence, respectively. In these analyses, the time-to-recurrence in the synthetic mesh group will be compared to the time-to-recurrence in the biologic mesh group using a two-sided log-rank test. The null hypothesis is that the time-to-recurrence is the same between the two groups (H0: Hazard Ratio = 1), and the alternative hypothesis is that the time-to-recurrence is significantly greater for the permanent synthetic mesh cohort compared to the biologic mesh cohort (H1: Hazard Ratio not= 1). Since this is a randomized clinical trial, observed differences in other covariates between the two study groups are assumed to arise by chance. Therefore, the simple unadjusted analysis is sufficient to answer the research question, assuming adequate power (see above). However, since the association between other covariates and time-to-recurrence may be of interest and because group imbalances may occur due to chance, it is of interest to consider further analyses that adjust for covariates in the relationship of time-to-recurrence and mesh type. To that end, the following multivariable models are pre-specified: 1) Demographics: age, race, gender, and study center; and 2) Known linkages to hernia

recurrence: BMI, history of smoking, size of defect (Hernia width), number of previous hernia repairs, and mesh type. These models will be fit with Cox proportional hazards models. The assumption of proportional hazard will be tested. When the proportional hazard assumption is violated, time dependent variables will be introduced to the model.

Post Hoc Additional Covariates:

Given Baseline differences in mesh width and length between the two groups, additional covariates were added to the model. Mesh Width was included

4.2 Statistical procedures for secondary outcomes

The secondary outcomes are quality of life (QOL) and Cost. The assessment of the association between these outcomes and mesh type will parallel what was described above for the primary outcome. The differences are as follows. First, the primary analysis will utilize an ANCOVA model adjusting for baseline pain (QOL) and correlations among repeated measurements. The null hypothesis is that the pain (QOL) is the same, on average, between the synthetic and biologic mesh groups (H0: Beta-mesh-type = 0). The alternative hypothesis is that the pain (QOL) is different, on average, between the two groups (H1: Beta-mesh-type not= 0). Second, the multivariable modeling will utilize linear regression models. A mixed model analysis with repeated measures will be performed to determine if a significant difference exists between the biologic mesh and the permanent synthetic mesh cohorts in the mean change in score from the preoperative assessment to the postoperative assessments at 1 month, 6 months, 12 months, and 24 months

for the EQ-5D and HerQLes quality of life instruments. The null hypothesis is that there is no significant difference between the biologic mesh and the permanent synthetic mesh cohorts in the mean change in score from the preoperative to the postoperative assessments at any of the time points for either the EQ-5D or the HerQLes quality of life instruments. The alternate hypothesis is that there is a significantly greater change in EQ-5D and HerQLes scores from the preoperative assessment to the postoperative assessment at each of the time points for the permanent synthetic mesh cohort compared to the biologic mesh cohort

To determine direct economic costs associated with clean-contaminated and contaminated open ventral hernia repair. Costs associated with the operative, and postoperative phases of care up to 30 days will be considered as it pertains to the management of the ventral hernia. Final operative costs will be based on each patient's actual inpatient encounter direct cost obtained from the participating institutions. Prosthetic mesh costs will also be extracted. Postoperative costs will account for routine outpatient visits, costs incurred for complications, up to 30 days due ventral hernia management. All costs will be reported in U.S. dollars.

Adverse events

Adverse events are reported throughout the trial and tabulations of all reported adverse events will be provided, subdivided by treatment group. Adverse events will be compared by 3 measures:

1. Overall adverse event rates
2. Clavien Dindo Grades I-V
3. Comprehensive Complications Index (Score 1-100)

Handling of missing data

Very little data is anticipated in the baseline demographics and operative details.

We anticipate up to a 20% lost to follow up for the primary analysis of 24 months hernia recurrence and SSOPI rates. Patients who died or were not available for follow up will be excluded from that time point analysis.