STOMA CLOSURE AND REINFORCEMENT (SCAR) TRIAL

A single center pilot study of the safety of a mesh reinforcement of ileostomy closure to prevent hernia formation in left sided colon and rectal cancer patients

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Study Products: Bard™ Soft Mesh (Bard Davol, Inc)

Protocol Number: D18101

NCT number: NCT03750461

Initial version: 11/10/17
Amended: 8/15/18
Amended: 10/19/18
Amended: 2/9/20

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List of Abbreviations

CCRC – Clinical Cancer Review Committee
DSMAC – Data Safety Monitoring and Accrual Committee
mL - Milliliter
MRSA – Methicillin-resistant Staphylococcus aureus
NCCC – Norris Cotton Cancer Center
NCCN – National Comprehensive Cancer Network
SSI – Surgical Site Infection
S-SSI - Superficial surgical site infection
D-SSI – Deep surgical site infection
O-SSI – Organ space surgical site infection
SCIP – Surgical Care Improvement Project
PDS – Polydioxanone
SSO – Surgical Site Occurance

Study Summary

Title	Stoma Closure and Reinforcement Trial (SCAR) – Pilot Study
Short Title	SCAR Trial
Protocol Number	1
Phase	Pilot feasibility
Methodology	Open Label
Study Duration	The study is estimated to last 5 years
Study Center(s)	Single center – Dartmouth Hitchcock Medical Center
Objectives	1. To perform a pilot study to validate the mesh implantation procedure at the time of ileostomy closure. 2. To evaluate patient satisfaction and resource utilization associated with the procedure. 3. To prospectively evaluate the cohort for evidence of hernia formation at the previous stoma site. 4. Use data from this trial to design an appropriately powered, multi-center, prospective randomized, controlled trial of mesh reinforcement of ileostomy closures.
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	1. Left sided colon or rectal cancer treated with resection and diverting loop ileostomy, with or without neoadjuvant or adjuvant therapy. 2. Age > 18years 3. Patient is undergoing elective closure of diverting loop ileostomy
Study Product, Dose, Route, Regimen	Bard™ Soft Mesh (Bard Davol, Inc): large pore, open weave, monofilament polypropylene mesh.
Duration of administration	The mesh would be implanted as a reinforcement of the stoma closure on a permanent basis. The mesh is not intended to be removed.
Reference therapy	Standard procedure for ileostomy closure
Statistical Methodology	No power calculation is necessary for this study since it is a pilot study. The results will be used to calculate power for future investigations.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Survival from colorectal cancer is continually increasing due to advances in multi-modality therapies leading to a growing cohort of patients with a history of the disease. Many of these patients will have long term complications from these treatments leading to a reduced quality of life. Minimally invasive approaches and enhanced recovery protocols have improved patient tolerance of colorectal cancer resection and reduced short term complications. Technologic improvements have allowed sphincter preserving surgery to be offered to a greater proportion of patients and therefore avoid permanent ostomies. However, temporary ostomies are often used as part of sphincter preserving surgery to minimize the consequences of a complication at a downstream anastomosis, and subsequently closed when clinically appropriate. Eventual restoration of intestinal continuity and closure of the ostomy puts patients at risk of developing a hernia at that site – a complication that occurs in approximately one third of patients[1-5]. What is not known is whether the strategies used to treat other types of abdominal wall hernias will be applicable in this situation due to its unique circumstances. There is a critical need to develop an intervention to reduce the incidence of hernia formation at the site of previous ostomies as these hernias at minimum reduce quality of life through chronic pain and disfigurement and at worst may require emergency surgery for intestinal obstruction. Without an improvement in technique, it is likely additional patients will experience this complication as the colorectal cancer survivor cohort grows.

Incisional hernias are common occurrence with an incidence ranging from 10 to 58%. [1,6] Risk factors include obesity, malnutrition, immunosuppression, connective tissue disorders, and previous abdominal surgery.[7-11] While some of these risk factors (like smoking) may be modifiable, others (such as the level of wound contamination) are not.[12] Although often amenable to minimally invasive approaches, colon and rectal procedures will frequently require a laparotomy type incision to extract bulky tumors.[13] Open procedures are unlikely to be entirely replaced by minimally invasive approaches in colorectal practice and these hernias will remain a significant clinical burden both for the patient and the clinician.

One such incisional hernia is particularly challenging: the hernia at the site of a prior intestinal ostomy.[1,3,4,6,14,15] The most common ostomy used for temporary intestinal diversion for colon and rectal cancer is the diverting loop ileostomy (herein referred to as ileostomy), which is an ostomy fashioned from the terminal segment of the small intestine. An ileostomy is used to protect a downstream anastomosis while patients heal or undergo adjuvant chemotherapy, and is preferred over colostomies due to the comparative ease of construction, ease of reversal, and a low rate of complications. They may be closed at a later time, as dictated by the patient's underlying disease process, restoring intestinal continuity. Hernias at the site of previous stoma placement are poorly understood, but are estimated to occur in up to a third of patients.[1-5]

Reinforcement of an ileostomy closure with mesh is a novel approach to addressing a clinical scenario that bears many similarities to an abdominal wall hernia. Ileum protrudes through a fascial defect but for the purposes of diversion of the fecal stream rather than as the result of a congenital condition or iatrogenic process in a previous surgical site. Primary repair of fascial defects, as is commonly performed for closure of ileostomy, is not well supported in the literature for repair of abdominal wall hernias because of an unacceptably high recurrence rate, reported at up to 43%.[16] Nearly all ostomies will have a fascial defect greater than 2cm which is where most surgeons would consider using mesh for a primary hernia repair such as an umbilical hernia.[17] Incorporating mesh, whether biologic or synthetic, decreases the failure rate of repair.[16] While underreported in the literature, most ostomies will have parastomal herniation of preperitoneal fat if not intraabdominal structures, indicating the ostomy defect has increased in size and adding further evidence to support addressing stoma takedown as a true hernia repair.[6] Historically, the data for repairing hernias argues against utilizing mesh in a contaminated or clean contaminated field due to concerns of significant complications such as infections, mesh erosion, bowel adhesions, fistula formation, and pain.[18-20] Biologic meshes have been used in these situations, with the prevailing theory being that biologics are more resistant to infection.[21,22] More recent data suggesting that sublay placement of a macroporous mesh of lightweight permanent or bioabsorbable

synthetic materials are relatively resistant to chronic infection challenge this notion, perhaps indicating the design and plane of implantation rather than material of the mesh are most important.[22-25] Other reports have suggested the safety of ventral hernia repairs with mesh placement concurrently with colorectal surgery.[26] Recent trial data have also suggested greater effectiveness in reduction of hernia recurrence at two years from time of repair compared to biologic mesh in similar wound classifications in addition to fewer wound occurrences in the post-operative period.[27] The cost advantages of macroporous and bioabsorbable mesh have also been reported as superior to biologic mesh.[28,29]

Anatomical positioning of the mesh during the hernia repair may also impact both the short term complications and the long term durability of the procedure. Three broad categories classify mesh placement: onlay, underlay, and sublay. Onlay is positioning of a mesh over a closed fascial incision in the subcutaneous space. Underlay is positioned within the peritoneal cavity beneath the closed fascial incision. The sublay (retro-rectus) position is within the muscular layers of the abdominal wall where fascial planes are closed on both sides of the mesh (Figure 1). Multiple reports have indicated intraperitoneal placement of mesh is associated with a higher recurrence rate compared to sublay or onlay techniques, with the sublay associated with the most favorable long term outcomes.[30-32]

Previous efforts to reduce formation of hernias have been described as having fair success, however they are limited by heterogeneity both in patient selection and in technique.[33-37] These studies have used suboptimal anatomic positioning of the mesh reinforcement and are further limited by lack of consideration of consistency of technique between surgeons and consideration of associated resource costs.

Quality of life after sphincter sparing surgery in colorectal cancer is highly variable and correlates to the proximity of the anastomosis to the anal canal, which is inversely proportional to amount of rectum removed.[38] Technologic advances has allowed more patients to undergo sphincter-preserving surgery than has previously been possible.[39] Given that most patients undergoing sphincter-preserving surgery for distal colorectal cancer will also undergo temporary proximal diversion, minimizing the quality of life reduction of this portion of the procedure is imperative. It is well known hernias are associated with a reduced quality of life.[40]

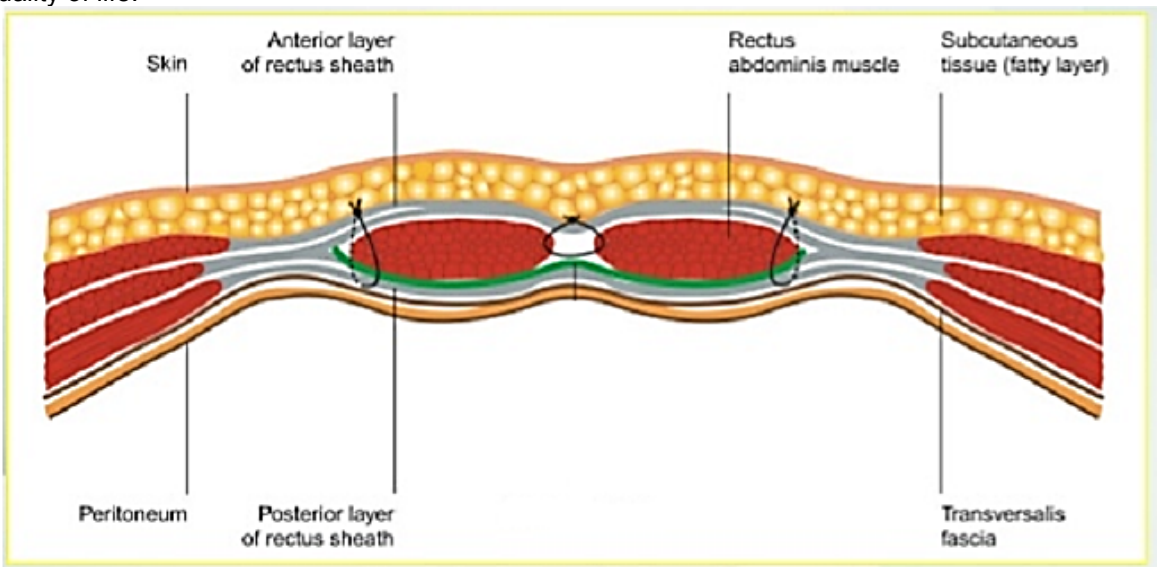

Figure 1. Sublay (Retro-rectus) placement of mesh (highlighted in green)

Our long-term goal is to develop a technique for closure of ostomy sites that minimizes the potential for hernia formation. The current literature is limited by a lack of prospective evaluation of the effectiveness of reinforcement of ostomy closure sites. Therefore, prospectively evaluating the technique will yield a more detailed understanding of how and when hernia formation at the ostomy closure site occurs and the presence of any unexpected findings. Our overall objectives in this study protocol, which is the first step towards our long-term-goal, are to (i) validate our ostomy site closure technique incorporating prosthetic mesh and calculate its associated costs, (ii) measure and compare patient reported quality of life pre- and post-intervention, and (iii) prospectively evaluate the incidence of hernia at

the stoma closure site at 6-months post procedure. Our central hypothesis is that a mesh reinforcement of the site during closure of an ostomy is safe and will reduce the incidence of hernia over time. The rationale for this project is that survival from colorectal cancer will continue to increase and improving the quality of life of patients by reducing long term complications of surgical therapy can be achieved through improvements in technique.

1.2 Investigational Device (Attachments A, B, C, D)

Bard™ Soft Mesh – is a light weight, woven, large open pore mesh made of polypropylene. It is an FDA approved product indicated for use in the reconstruction of soft tissue defects.

1.3 Clinical Data to Date

Multiple clinical studies have been conducted regarding implantation of mesh to reinforce abdominal wall defects and this is widely accepted among surgeons who treat hernias.[16,17,30] Light weight polypropylene mesh, specifically implanted in the identical anatomical position as proposed by this study has been studied extensively in the treatment of ventral hernias and found to be safe and effective.[23,24,31,32,41] Furthermore, a large scale, multiple institution trial using this specific mesh, and ones of similar design and construction marketed by other manufacturers, implanted in the same anatomic location under the same levels of wound contamination found acceptable infection and hernia recurrence outcomes.[23]

1.3.1 Safety Events

The previously referenced trial reported an overall 31% incidence of surgical site occurrences (SSO), which were defined as any surgical infection, wound dehiscence, wound breakdown, enterocutaneous fistula, seroma/hematoma formation, wound cellulitis, suture abscess, or nonhealing wound as described by the Ventral Hernia Working Group.[42] The criteria for 30-day SSI was taken directly from the CDC criteria and was categorized into superficial, deep, and organ space infections. This included 7% wound dehiscence rate, 5% incidence of seroma or hematoma, 4% wound cellulitis rate, and a 1% enterocutaneous fistula rate. The SSI rate was (14%) where S-SSI was 8%, D-SSI was 3%, and O-SSI was 3%. In their cohort, only 4% of patients required mesh removal.[23] These findings are consistent with other reports of similar studies.[26,27]

1.4 Risk/Benefits

The primary concern is for surgical site occurrences. In the absence of mesh, the incidence of infection in ileostomy closures is estimated between 6 and 18%.[43-45] This rate is minimized with the use of a purse string skin closure with iodine impregnated gauze packing vs partial closure with an open ended drain (Penrose type) or primary skin closure.[46] Prospective trial data estimates the overall incidence of infections when bioabsorbable mesh is placed in Class II and III ventral hernia repairs at 18%. None required mesh explantation and all wounds eventually healed.[27] Other reports of macroporous polypropylene mesh in clean-contaminated and contaminated wounds suggest an infection rate of 7.1% for clean contaminated and 19% for contaminated cases. [23] Surgical site occurrences will be treated on an individual patient basis determined by the clinical consequences of the occurrence. Infection may potentially be treated with antibiotics, local wound care, operative debridement, radiographically guided drainage procedures, vacuum assisted wound closure devices, or mesh removal at the discretion of the study team. Other potential adverse events are those inherent to intestinal surgery; anastomotic leak, peritoneal abscess formation, bowel obstruction, or ileus, in addition to the risks associated with general anesthesia.

2 Study Objectives

Primary Objective: To validate the technical procedure of mesh implantation at the time of ileostomy closure and preliminarily determine the incidence of surgical site occurrences (particularly those requiring intervention) compared to standard ileostomy closure technique.

Secondary Objective #1: Measure and compare quality of life scores for aspects related to the procedure to those related to bowel function.

Secondary Objective #2: To evaluate the process for longitudinally monitoring for the occurrence of hernia at site of stoma closure. We will evaluate our study protocol for the feasibility of performing a larger trial by measuring recruitment, retention of patients, adherence to the study protocol, and process assessment.

By the completion of this pilot study, our expected outcomes are to have demonstrated a high level of procedural fidelity among the operating surgeons of the modified ostomy closure technique and comparable costs to the standard procedure as well as greater than 80% recruitment and retention of eligible participants, and greater than 90% adherence to the study protocol. We also expect to preliminarily demonstrate safety and similar quality of life compared to historical controls on short term follow-up. These results are expected to inform development of an appropriately powered, multiple center, randomized controlled trial comparing the effectiveness of our novel modification of ostomy closure technique to the standard technique.

3 Study Design

3.1 General Design

This is a pilot study evaluating the feasibility of a novel modification to an established surgical procedure. The three operating surgeons are faculty members of the Division of Colon and Rectal Surgery in the Department of Surgery at DHMC. All radiographs will be reviewed by a single faculty of the Department of Radiology. We will use a modified Simon Two stage approach, the first phase will include five patients treated and followed sequentially. If there are 1 or fewer major wound occurrences (those requiring return to the operating room) then the study will proceed to the second phase which will include a total of 15 patients followed concurrently.

3.2 Primary Study Endpoints

The primary end point of the study is the validation of the mesh implantation procedure. We will assess the incidence of wound occurrences (defined as S-SSI, D-SSI, organ space SSI, dehiscence, and seroma formation) at 30days, with particular attention to wound occurrences requiring procedural intervention, including but not limited to, operative debridement, radiographically guided drain placement, or excision of the mesh. These incidences will be compared to historical controls.

3.3 Secondary Study Endpoints

The secondary endpoints will be evaluation of the incidence of hernia formation at the ileostomy site on a prospective basis at 30 days and 6 month intervals thereafter until two years from the date of ileostomy closure. The Promis SF 2.0 8a Ability to Participate in Social Roles and Activities instrument will be used to assess quality of life and the Colorectal Functional Outcome (COREFO) instrument will be used to evaluate bowel function at each interval.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Age > 18years
2. Patient is undergoing closure of loop ileostomy
3. Patient has a diagnosis of left sided colon or rectal cancer treated with resection and diverting loop ileostomy
4. Patient has been evaluated by a qualified surgeon and found to be a suitable candidate for surgery

4.2 Exclusion Criteria

1. Pre-existing systemic infection at the time of ileostomy takedown
2. Cirrhosis, chronic renal failure requiring dialysis, or collagen disorder
3. On current immunosuppression (anti-TNF agents, chemotherapy, or prednisone >10mg/day)
4. Previous abdominal hernia repair with mesh placement
5. Concurrent procedures in addition to closure of diverting loop ileostomy
6. Ileostomy closure not completed through the previous stoma site (i.e. those requiring exploratory laparotomy for closure)

4.3 Subject Recruitment and Screening

Study subjects will be recruited from the Dartmouth Hitchcock Department of Surgery, Division of Colon and Rectal Surgery clinical practice. Patients will be deemed eligible for the study based upon clinical indicators for appropriateness of ileostomy closure.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Patients may be withdrawn from the study at any time based upon withdraw of consent. Patients may also be withdrawn if the study treatment cannot be tolerated (i.e. removal of mesh device is required). Patients must continue to participate for 30days post-operatively in order for inclusion in the analysis of the primary endpoint data.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Data related to the time period of the subject's participation will be included in the analysis of the treatment effect. Should a subject be withdrawn from the study for any reason, survival data will be maintained in accordance with the guidelines for follow-up prescribed by the NCCN.

5 Study Procedures

5.1 Encounter 1

Patients will be assessed for ileostomy closure based upon completion of therapy after primary resection of their malignancy. Appropriate candidates will be determined at the operating surgeon's discretion based on customary evaluation of clinical status. The informed consent process will be initiated and the patient recruited into the study.

5.2 Encounter 2

This encounter is the operative procedure. The procedure for closing the ileostomy (i.e. bowel anastomosis) will be at the discretion of the surgeon, provided it is performed through the ileostomy site without additional laparotomy incisions. In accordance with SCIP guidelines, pre-operative intravenous antibiotic and subcutaneous pharmacologic venous thromboembolism prophylaxis will be administered. Patients with a history of MRSA infection will also receive a dose of intravenous vancomycin prior to the procedure.

The abdominal wall reconstruction portion of the procedure will be standardized to ensure consistency between surgeons. The posterior rectus sheath is closed with native tissue either primarily, using hernia sac if present, or bridged with Vicryl-type mesh and a quickly absorbing suture material. This is done to isolate the mesh from the peritoneal cavity. The retrorectus plane is developed using electrocautery and blunt dissection to provide adequate placement of mesh such that it overlaps the posterior sheath defect by a minimum of 3cm on all sides. The mesh is placed in this plane and secured in place with slowly absorbable monofilament (0-PDS preferred) sutures placed through the anterior fascia or with application of fibrin sealant at the surgeon's discretion. This space is then irrigated with

250mL of bacitracin/neomycin/polymixin antibiotic solution, patients with a history of MRSA will have vancomycin added to this solution. The anterior rectus sheath is then closed in a running fashion with slowly absorbing monofilament suture (0-PDS preferred). Again, 250mL of antibiotic solution are used as irrigation. A closed suction drain may be left in the retrorectus space at the discretion of the surgeon. Scarpa's layer is closed if possible and then skin closed with a circumferential purse string absorbable suture and the subcutaneous cavity packed with Iodoform gauze. This gauze is then removed on post-operative day 2. Post operatively the patient will receive standard care.

5.3 Encounter 3, 4, 5, et al.

The patients will be seen at 30days following discharge from hospitalization for stoma closure for a clinical examination and then will undergo standard follow-up for their cancer surveillance in accordance with NCCN guidelines which include computed tomography imaging every 6 months. Concurrently, clinical cancer surveillance evaluation by the operating surgeon (in conjunction with surveillance visits by medical oncology) will be performed on the same schedule with evaluation of clinical evidence of hernia formation as well as assessment of patient experience with the stoma site as part of regular cancer surveillance visit. These images will be subsequently evaluated for radiographic evidence of hernia formation by a radiologist blinded to the presence of the mesh, which is radiolucent. Patients will be undergoing computed tomography evaluation primarily as part of their cancer surveillance, and this imaging is not obtained expressly for the purposes of this study, and are only secondarily utilized to screen for hernia occurrence. Patients will also undergo ultrasound examination of the ostomy closure site at 30d post operatively then on the same 6 month schedule. These images are obtained for the purposes of the study and are intended to be compared to the computed tomography findings to evaluate congruence of the two modalities. These visits occur on a prescribed schedule for a period of 5 years after cancer treatment has concluded, after which no further follow-up is required.

Sonographic evaluation of the stoma site will be obtained on the Supersonic Unit in the Advanced Imaging Center using an 8-15 mHz linear transducer.

Cine clips will include all margins of the mesh repair to ensure adequate coverage of the repair site.

SUPINE:
Patients will initially be examined in the supine position.

1. Longitudinal and Transverse images of the stoma site will be obtained with normal breathing followed by a video clip in long or transverse plane.
2. Longitudinal and Transverse images of the stoma site will be obtained with Valsalva maneuver followed by a video clip in long or transverse plane with Valsalva.
3. If a stoma site hernia is identified, measurements of the abdominal wall defect will be obtained with and without Valsalva.
4. If a stoma site hernia is identified Longitudinal and Transverse images of the stoma site will be obtained with transducer compression followed by a video clip in long or transverse plane.

STANDING:
Patients will then be examined in the standing position.

1) Longitudinal and Transverse images of the stoma site will be obtained with normal breathing followed by a video clip in long or transverse plane.
2) Longitudinal and Transverse images of the stoma site will be obtained with transducer compression followed by a video clip in long or transverse plane.
3) If a stoma site hernia is identified on standing views only, measurements of the abdominal wall defect will be obtained with and without Valsalva.

4) If a stoma site hernia is identified on standing views only, Longitudinal and Transverse images of the stoma site will be obtained with transducer compression followed by a video clip in long or transverse plane.

6 Statistical Plan

6.1 Sample Size Determination

6.2 This is a pilot study and therefore the anticipated number of patients included (20) represents an attainable number within the planned study period (1 year) based on the clinical volume of our group. Our group treats approximately 35-40 patients per year who would likely meet inclusion criteria for this trial. We estimate a cohort of 200 patients in a randomized trial will be required to demonstrate superiority of the technique, and a 10% sample of that cohort will be sufficient provide preliminary safety data as well as to demonstrate feasibility of a future trial.

6.3 Statistical Methods

The results of this study will be compared using a univariate analysis to historical control data obtained from the DHMC ACS-NSQIP database, with emphasis on surgical site occurrences including all types of SSI, and unplanned return to the operating room data points. The preliminary safety and feasibility data obtained from this study will be used to inform design of a larger study to test the hypothesis that the procedure can obtain a 50% reduction in the incidence of hernia formation at previous ileostomy sites compared to rates reported in the literature. The secondary objectives have not been previously reported in the literature either for patient reported outcomes or prospective evaluation of hernia formation. Further work, based on the data from this study, will attempt to show the superiority of the technique over currently used closure techniques as well as patient satisfaction with the procedure.

6.4 Subject Population(s) for Analysis

The statistical analysis for this study will use an all-treated population: Any subject who participated in the study and underwent the study procedure. Patients without complete follow-up data will be excluded from the final analysis.

7 Safety and Adverse Device Effects

7.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- <u>Suggests that the research places subjects or others at greater risk of harm</u> (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests

- is considered by the investigator to be of clinical significance

Unanticipated Adverse Device Effect (UADE):
An unanticipated adverse device effect is any serious adverse effect on health or safety, or any life-threatening problem or death, caused by or associated with an investigational device. Internal Unanticipated Adverse Device Effects (UADE) reports must be made within 10 working days.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 90 days following hospital discharge from the ileostomy closure procedure

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

7.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis. The monitoring period for Serious Adverse Events (SAE) will continue for 6 months after the study procedure.

All adverse events, including those possibly related, occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

7.3 Reporting of Unanticipated Adverse Device Effects and Unanticipated Problems

Investigators and the protocol sponsor must conform to the reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- Related, or possibly related, to study participation,
- unexpected, and
- serious or involve risks to subjects or others
  (see definitions, section 7.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

7.3.1 Investigator reporting: notifying the Dartmouth IRB

This section describes the requirements for safety reporting by investigators who are Dartmouth faculty, affiliated with a Dartmouth research site, or otherwise responsible for safety reporting to the Dartmouth IRB. The Dartmouth College IRB (CPHS) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Dartmouth IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Dartmouth IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

AND

Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process
Unanticipated problems posing risks to subjects or others as noted above will be reported to the Dartmouth IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation). Internal Unanticipated Adverse Device Effects (UADE) reports must be made within 10 working days.

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

7.4 Stopping Rules

1. Should a patient participating in the study suffer an adverse event resulting in mortality or severe morbidity such as necrotizing infection or sepsis as a result of mesh infection, the trial will be suspended pending an investigation by the Principal Investigator and the co-investigators as to whether the procedure or prosthetic mesh was the inciting cause of the adverse effect.
2. Should a patient require return to the operating room for treatment of a wound occurrence requiring removal of the mesh, the trial will be suspended pending investigation of the case to determine the cause of the wound occurrence as well as to evaluate the necessity of modification of the protocol to avoid similar occurrences in future patients.
3. If either of the above conditions occur, in addition to stopping the trial, both the CPHS and NCCC DSMAC will be promptly notified.

7.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the implementation of a site data and safety-monitoring plan (see Section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of unanticipated adverse device effects.

8 Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

8.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

8.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

8.4 Records Retention

Data related to the study subjects and the trial will be maintained for a minimum of 5 years following the procedure. This data will be secured using the Velos eResearch Database.

9 Study Monitoring, Auditing, and Inspecting

9.1 Safety and Data Monitoring

This study will be monitored by the Data Safety Monitoring and Accrual Committee (DSMAC) of the Norris Cotton Cancer Center. It is a multidisciplinary committee charged with overseeing monitoring of safety of participants, conduct, progress, and validity and integrity of the data of all clinical trials at NCCC at Dartmouth. The Committee meets quarterly to review accrual rates and information for studies that have accrued participants. The Clinical Cancer Review Committee (CCRC) determines the frequency of DSMAC data and safety review. This protocol will be reviewed on a quarterly basis. The DSMAC has the authority to suspend or to recommend termination to the CCRC of all research activities that fall within its jurisdiction. In the event that a study is suspended or terminated, that information will be forwarded to the CPHS (Dartmouth IRB) office.

9.2 On-Site Monitoring

9.3 Clinical research monitoring for regulatory compliance and data integrity will be conducted according to the NCI-approved NCCC Data and Safety Monitoring Plan. Internal monitoring is conducted by appropriately trained staff of the NCCC Office of Clinical Research and Dartmouth-Hitchcock Medical Center Clinical Trials Office who are not involved in the study. This monitoring will include periodic assessment of the regulatory compliance, data quality, and study integrity. Study records will be reviewed and directly compared to source documents and the conduct of the study will be discussed with the investigator. Monitors may request access to all regulatory documents, source documents, CRFs, and other study documentation for on-site inspection. Direct access to these documents is guaranteed by the investigator, who must provide support at all times for these activities. Auditing and Inspecting

10 Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities, and applicable Dartmouth and institutional compliance and quality assurance offices. Investigators will permit study-related audits and inspections by the Dartmouth and local IRB,

CTO Clinical Trials Office, government regulatory bodies, and Dartmouth-Hitchcock or institutional compliance and quality assurance groups of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.) The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., diagnostic laboratory).Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment A for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11 Study Finances

11.1 Funding Source

This study not industry sponsored and is financed through the career development funds of the primary investigator or non-industry grant funding.

11.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Dartmouth investigators will follow the Dartmouth conflict of interest policy.

12 Publication Plan

The publication of results will follow a stepwise progression. The first publication will detail the protocol of the trial and the results of the pilot study. Secondary publications are planned to address the costs of the intervention, patient reported outcomes and satisfaction. Later publications will detail the results of the planned multicenter trial comparing standard ostomy closure techniques to the intervention.

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

13 References

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14 Attachments

A. Bard Soft Mesh Marketing Information
B. Bard Soft Mesh Package Insert
C. Bard Soft Mesh Packaging
D. Bard Soft Mesh 510(k) Documentation