Title: STOMA CLOSURE AND REINFORCEMENT (SCAR)-II TRIAL

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PROTOCOL TITLE:

STOMA CLOSURE AND REINFORCEMENT (SCAR)-II TRIAL
A single center pilot study of the safety of a mesh reinforcement of ileostomy closure to prevent hernia formation in Inflammatory Bowel Disease patients

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	2/9/2021	Updated consent to provide details on bioabsorbable mesh Updated protocol to provide further details on short-term data from SCAR-1	yes
2	5/5/2021	Revise ultrasound section	yes
3	5/14/2021	Revise ultrasound section back to AIC	yes
4	11/10/21	Update visit windows to include +/- days	no

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1.0 Study Summary

Study Title	Stoma Closure and Reinforcement Trial (SCAR)-II
Study Design	Cohort
Primary Objective	1. To perform a pilot study to evaluate the incidence of wound occurrences associated with resorbable biosynthetic mesh placement in the study cohort.
Secondary Objective(s)	1. To prospectively evaluate the cohort for evidence of hernia formation at the previous stoma site. 2. To evaluate patient satisfaction and resource utilization associated with the procedure.
Research Intervention(s)	Mesh placement within the abdominal wall at the time of ostomy closure as a tissue reinforcement
Study Population	Patients diagnosed with Crohn's and Ulcerative Colitis
Sample Size	20
Study Duration for individual participants	Approximately 6 months.
Study Specific Abbreviations/ Definitions	MRSA – Methicillin-resistant Staphylococcus aureus P4HB – Poly-4-hydroxybutyrate 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 Occurrence

2.0 Objectives*

2.1 Primary Objective: To perform a pilot study to evaluate the incidence of wound occurrences associated with resorbable biosynthetic mesh placement in the study cohort.

2.2 Secondary Objective #1: To prospectively evaluate the cohort for evidence of hernia formation at the previous stoma site.

2.3 Secondary Objective #2: To evaluate patient satisfaction and resource utilization associated with the procedure.

2.4 Hypothesis: Our central hypothesis is that a resorbable biosynthetic 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 the IBD patient cohort will continue to increase as medical therapies continue to improve and improving the quality of life of patients by reducing long term complications of surgical therapy can be achieved through improvements in technique. 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.

3.0 Background*

3.1 Treatment for inflammatory bowel disease (IBD, Crohn's and Ulcerative Colitis) is continually evolving with 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, particularly surgical treatment, leading to a reduced quality of life. Minimally invasive approaches and enhanced recovery protocols have improved patient tolerance of bowel resection for complications of IBD and reduced short term complications. Technologic improvements have allowed bowel and 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 these approaches 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, potential fistulization, 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 IBD 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 [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 IBD related surgery is the diverting loop ileostomy (herein referred to as ileostomy), which is an ostomy fashioned from an appropriate segment of the small intestine. An ileostomy is used to protect a downstream anastomosis while patients heal from surgery and correct any pre-existing nutritional abnormalities or wean from steroid therapy. 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 [38].

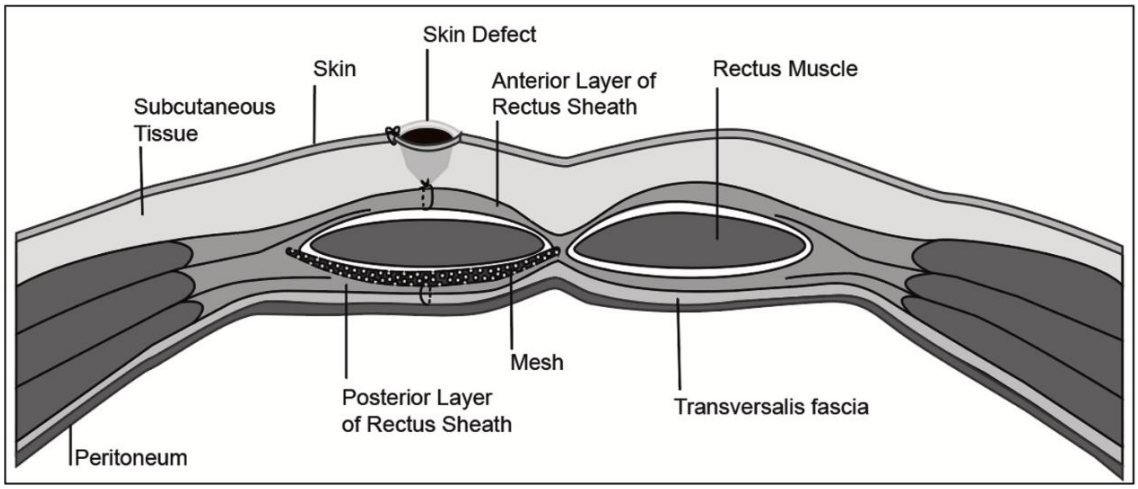

Fig. 1. Retro-rectus placement of mesh in abdominal wall.

Recently, the preliminary safety data from the SCAR-I trial (ClinicalTrials.gov Identifier: NCT03750461) has demonstrated no early adverse events with respect to mesh implantation at the time of ileostomy reversal in any of the twenty patients studied. Specifically, there have been zero incidences of infection or hernia formation at 30 days post-operatively.

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.

4.0 Study Endpoints*

4.1 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 30 days, 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

4.2 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 at 6 months 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.

4.3 Primary Safety Endpoints: 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.

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.

If either of the above conditions occur, in addition to stopping the trial, the D-HH Office of Research Operations will be notified.

5.0 Study Intervention/Investigational Agent

5.1 Investigational Agent: Phasix™ Soft Mesh – a knitted monofilament mesh scaffold using Poly-4-hydroxybutyrate (P4HB), a biologically derived material. It is an FDA approved product indicated to reinforce soft tissue where weakness exists in patients undergoing plastic and reconstructive surgery, or for use in procedures involving soft tissue repair, such as the repair of hernia or other fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result.

5.2 Receipt of supplies and storage: The Phasix™ Soft Mesh is already available and in stock in the DHMC operating rooms and will be stored according to standard OR protocols.

6.0 Procedures Involved*

6.1 Study 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. Alternatively, if the results from the SCAR-I trial (actively accruing) are available at the start of SCAR-II enrollment and are without safety concerns, we will enroll 20 patients sequentially in a one stage approach.

6.2 Encounter 1: Patients will be assessed for ileostomy closure based upon degree of healing from surgery, correction of any pre-existing nutritional abnormalities, and ability to wean from steroid therapy. 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.

6.3 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 circumferentially. 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 thoroughly irrigated with of 0.05% chlorhexidine gluconate (CHG) solution, patients with a history of MRSA will receive a dose of IV vancomycin pre-operatively. The anterior rectus sheath is then closed in a running fashion with slowly absorbing monofilament suture (0-PDS preferred). Again, (volume) of the CHG solution is 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.

The ileostomy reversal will be performed in an accepted standard of care fashion and the abdominal wall reconstruction will be performed exactly as specified by the protocol outlined above. The combination of these two entities will lessen the probability and magnitude of risk.

6.4 Encounter 3 and 4.: The patients will be seen at 30 days (+/- 2 weeks) following discharge from hospitalization for stoma closure for a clinical

examination. Concurrently, evaluation of clinical evidence of hernia formation as well as assessment of patient experience with the stoma site will be performed. Patients will also undergo ultrasound examination of the ostomy closure site at 30d (+/- 2 weeks) and 6 months (+/- 30 days) post operatively.

Sonographic evaluation of the stoma site will be obtained in the Advanced Imaging Center under the supervision of Dr. Roberta diFlorio-Alexander. Cine clips will include all margins of the mesh repair to ensure adequate coverage of the repair site. Specific images to be captured are as follows:

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.

7.0 Sharing of Results with Subjects*

7.1 Study results will not be shared with subjects. The ultrasounds are being done only for purposes of the study. The results will be read by Dr. diFlorio-Alexander, but not shared with individual research subjects or uploaded to their medical record. If the ultrasound examination reveals a health concern, the subject will be referred for appropriate clinical follow up.

8.0 Study Timelines*

8.1 Duration of individual subject's participation: Each subject will be participating in the study for a period of ~ 6 months, from encounter 1 (pre-operative visit) to encounter 3 (6-month ultrasound surveillance visit).

8.2 The duration anticipated to enroll all study subjects: The study is estimated to last 3 years from time of first enrollment.

9.0 Subject Population*

9.1 Inclusion Criteria

1. Age > 18years.

2. Patient is undergoing closure of loop ileostomy.

3. Patient has a diagnosis of Inflammatory bowel disease 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.

9.2 Exclusion Criteria

1. Pre-existing systemic infection at the time of ileostomy takedown
2. Cirrhosis, chronic renal failure requiring dialysis, or collagen disorder
3. Previous abdominal hernia repair with mesh placement
4. Concurrent surgical procedures in addition to closure of diverting loop ileostomy
5. Ileostomy closure not completed through the previous stoma site (i.e. those requiring exploratory laparotomy for closure)

9.3 Specifically Excluded Populations

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

10.0 Vulnerable Populations*

10.1 Not Applicable

11.0 Local Number of Subjects

11.1 The study intends to recruit 20 patients at DHMC.

12.0 Recruitment Methods

12.1 Patients will be recruited from the clinical practice of the Dartmouth Hitchcock Department of Surgery, Division of Colon and Rectal Surgery.

12.2 Patients will be seen as referrals from the DHMC Division of Gastroenterology as well as providers outside the DH system.

12.3 Patients will be deemed eligible for the study based upon clinical indicators for appropriateness of ostomy closure based upon clinical indicators for the appropriateness of ostomy closure.

12.4 There is no financial compensation to study subjects

13.0 Withdrawal of Subjects*

13.1 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 30 days post-operatively in order for inclusion in the analysis of the primary endpoint data.

13.2 Data related to the time period of the subject's participation will be included in the analysis of the treatment effect.

14.0 Risks to Subjects*

14.1 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%.[39-41] 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.[42] 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.

15.0 Potential Benefits to Subjects*

15.1 Potential benefits to participants include possible decreased likelihood of developing a stoma-site hernia in the future and avoidance of another operation.

16.0 Data Management* and Confidentiality

16.1 Sample Size Determination: This is a pilot study and therefore the anticipated number of patients included (20) represents an attainable number within the planned study period (3 years) 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.

16.2 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.

16.3 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.

16.4 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.

16.5 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.

16.6 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.

16.7 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.

17.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

17.1 Safety and Adverse Device Effects:

- **Definitions**:
  - Unanticipated Problems Involving Risk to Subjects or Others: Any incident, experience, or outcome that meets all of the following criteria:
    a. Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.

b. Related or possibly related to participation in the research (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)

c. Suggests that the research places subjects or others at greater risk of harm (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:

  a. results in study withdrawal

  b. is associated with a serious adverse event

  c. is associated with clinical signs or symptoms

  d. leads to additional treatment or to further diagnostic tests

  e. 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:
  a. The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
  b. The abnormality suggests a disease and/or organ toxicity
  c. 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:
  a. 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.

b. Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.

c. 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.

17.2 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 be 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.

17.3 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
- 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

17.4 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 Hitchcock IRB 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.

17.5 Stopping Rules:

- 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.
- 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.
- If either of the above conditions occur, in addition to stopping the trial, the D-HH IRB will be notified.

17.6 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. Medical monitoring will include a regular assessment of the number and type of unanticipated adverse device effects.

17.7 Safety and Data Monitoring:

The preliminary safety data from the SCAR-I trial (ClinicalTrials.gov Identifier: NCT03750461) has demonstrated no early adverse events with respect to mesh implantation at the time of ileostomy reversal; specifically there have been zero incidences of infection. Given these findings, the level of risk associated with the study intervention in the SCAR-II trial does not warrant oversight from an external DSMB.

17.8 On-Site Monitoring:

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).

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.

18.0 Provisions to Protect the Privacy Interests of Subjects

18.1 Study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

18.2 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.

19.0 Compensation for Research-Related Injury

19.1 There will be no monetary compensation in the event of research related injury.

20.0 Economic Burden to Subjects

20.1 Study subjects will be responsible for expenses related to travel to and from DHMC for their pre-operative, and post-operative care. The only additional

expense to the subjects related to the study is travel expenses for the 4th encounter (6-month sonographic evaluation). All other travel expenses would be the same for a standard ileostomy reversal.

20.2 Study subjects and/or their insurance will be responsible for the cost of the surgical procedure.

20.3 The mesh is provided by B-D.

20.4 The ultrasounds will be paid for by the study and not billed to the subjects or their insurance.

20.5

21.0 Consent Process

21.1 Consent will be ascertained at the pre-operative clinic visit following the "SOP: Informed Consent Process for Research (HRP-090)."

21.2 Non-English-Speaking Subjects:

- If subjects are eligible to participate and do not speak English, a DH translator will be present for the clinic visit and to review the consent in its entirety.

21.3 Cognitively Impaired Adults and Adults unable to consent:

- If a cognitively impaired adult or an adult whom is unable to consent is eligible for participation, the procedure and consent ill be reviewed with a representative for the patient using the following order: durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child.

21.4 Consent will be ascertained from all study participants and the consent document will be stored with the subject's medical record.

22.0 Process to Document Consent in Writing

22.1 Consent will be documented in writing (Appendix A). The "SOP: Written Documentation of Consent (HRP-091)" will be followed.

23.0 Setting

23.1 All research activities will be conducted at DHMC.

23.2 Patients will be recruited from the clinical practice of the Dartmouth Hitchcock Department of Surgery, Division of Colon and Rectal Surgery.

23.3 Patients will be seen as referrals from the DHMC Division of Gastroenterology as well as providers outside the DH system.

23.4 Resources Available:

- The recruitment and enrollment of 20 subjects will serve as a pilot study for a future multicenter RCT. The 20 subjects represent 10% of proposed future enrollment.
- The study team will devote ~1 business day per week related to research activities
- All personnel involved with the research are continuously updated on changes to the protocol, procedures, and what their responsibilities are. All members of the team are CITI certified and will maintain credentialing throughout the study period.

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