

SAFE-2023 Colovac 2 Study Clinical Investigation Plan



SAFE (SafeHeal Anastomosis Evaluation)-2023 Study: A Study to Investigate the Performance and Safety of the Colovac 2 Colorectal Anastomosis Protection Device

SAFE-2023 Study Protocol

Version 3

4 December 2024

Sponsor:

SafeHeal SAS

9 rue du 4 Septembre

75002 Paris, France

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Signatures:

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The Sponsor and the Principal Investigator have approved the Clinical Investigation Plan SAFE-2023 revision 3 (dated 4 December 2024) and confirm hereby to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155, ICH-GCP as far as applicable, and the local legally applicable requirements.

Sponsor:

SafeHeal Inc.
1501 W. Cleveland Street
Suite 200
Tampa, FL 33606

Signed by: *Heather Cronin* 09-Dec-2024
6117D3DF578F4EA...

Heather Cronin, SafeHeal, VP Clinical Affairs Date

I have read and understand this CIP and agree that it contains all the information required to conduct the study. I agree to conduct the study as set out in this CIP. In particular, I agree to adhere to the moral, ethical and scientific principles governing clinical research as set out in the current versions of the Declaration of Helsinki and the guidelines on Good Clinical Practice, accepting the oversight of the monitor and control procedures including direct access to source documents. I also agree to meet the applicable regulatory requirements.

Principal Investigator:

Name: _____

Address: _____

Principal Investigator Signature

Date

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2.0 Protocol Synopsis

Title	SAFE (SafeHeal Anastomosis Evaluation)-2023 Study: A Study to Investigate the Performance and Safety of the Colovac 2 Colorectal Anastomosis Protection Device
Investigational Device	Colovac 2: Colorectal Anastomosis Protection Device following Low anterior resection (LAR) for colorectal cancer. The Colovac 2 System includes the Colovac 2 Colorectal Anastomosis Protection Device and the SafeHeal Vacuum Management Device (Smartvac). The Colovac 2 Device includes the Colovac 2 Implant (stent and sheath) and the Colovac 2 Introducer.
Study Design	This is a prospective, single arm study to evaluate the usability, and preliminary safety and effectiveness of the Colovac 2 - Colorectal Anastomosis Protection Device at Day 10 post-implantation. Subjects will be followed through 4 weeks after surgery to document the longer-term status of the anastomosis and any significant safety event post-discharge. All performance, safety and effectiveness endpoint analyses will include data collected through Day 10.
Sample Size	Up to 50 subjects
Proposed Indication for Use for the Study	The SafeHeal Colovac 2 Device is intended for use in patients requiring low anterior rectal anastomoses to limit stoma creation to only those patients requiring more time for anastomosis healing when the device is removed, allowing patients with a healed anastomosis to avoid stoma creation.
Sponsor	SafeHeal SAS 9 rue du 4 Septembre, 75002 Paris, France
Number of Sites	Up to 3 sites
Number of Subjects	Up to 50 Investigational (Colovac 2) Subjects
Study Treatment	Colovac 2 Device implantation after colorectal resection for colorectal cancer
Objectives	<p>The primary objective of the study is to assess the clinically significant migration rate of the device through post-procedure Day 10 when the device is removed.</p> <p>The secondary objectives of the study are to assess the:</p> <ul style="list-style-type: none"> • Preliminary safety and performance of the Colovac 2 System • Ease of use the Colovac 2 Colorectal Anastomosis Protection Device • Ease of use of the Colovac 2 Introducer and Implant and Vacuum Management Device
Primary Performance Endpoints at Day 10	The primary performance endpoint is the clinically significant migration rate of the Colovac 2 device during its 10-day implantation period.
Other Performance Endpoints at Day 10	<ul style="list-style-type: none"> • Clinically significant migration rate • Ostomy avoidance rate • Cleanliness of colon immediately prior to device retrieval
Safety Endpoints at Day 10	<ul style="list-style-type: none"> • Mucosal appearance at anchoring site after device removal • Device related complications • All complications
Safety Evaluation	All adverse events will be collected for all subjects. An independent Clinical Evaluation Committee (CEC) will review events according to the CEC Charter.

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Inclusion Criteria	<p>A subject meeting all of the following criteria will be considered for participation in the study:</p> <ol style="list-style-type: none"> 1. Adult patients (18 years of age or older) 2. Eligible to undergo open or minimally invasive sphincter-sparing colorectal resection with planned diverting loop ileostomy for malignancy, based on multidisciplinary team recommendations 3. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2 4. Willingness to comply with protocol-specific treatment and study visits and to sign a written Informed Consent Form
Exclusion Criteria	<p>A subject meeting any of the following criteria will not be considered for participation in the study:</p> <p><u>Preoperative</u></p> <ol style="list-style-type: none"> 1. History of left sided colitis 2. Known allergy to nickel or other components of the Colovac 2 System 3. Pregnant or nursing female subject 4. Concomitant major surgical procedure in combination with Colorectal resection (i.e., hepatectomy) 5. Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation, impair the ability of the participant to undergo protocol described procedures or interfere with the interpretation of study results including, but not limited to: <ol style="list-style-type: none"> a) Stage IV colorectal cancer unless curative intent R0 resection is planned AND there is no associated peritoneal disease b) Immunodeficiency (CD4+ count < 500 CU MM) c) Systemic steroid therapy within the past 6 months d) Systemic infection at the time of surgery or requiring systemic antimicrobial therapy up to 1 week before surgery e) Major surgical or interventional procedures within 30 days prior to this study or planned surgical or interventional procedures within 30 days of entry into this study f) Diagnosis of bowel obstruction, bowel strangulation, peritonitis, bowel perforation, intraabdominal infection, ischemic bowel, carcinomatosis g) Fecal incontinence, involvement of sphincter by the neoplastic disease or evidence of extensive local disease in the pelvis seen on pre-operative imaging h) Severe malnutrition defined as 10% weight loss within 3 months prior to enrollment. 6. The subject is currently participating in another investigational drug or device study <p><u>Intraoperatively</u></p> <ol style="list-style-type: none"> 7. Anastomosis placement above the sacral promontory 8. Occurrence of any of the following during the colorectal surgery: <ol style="list-style-type: none"> a) Blood loss (>750 cc) b) Blood transfusion c) Any new sign of ischemia d) Positive air leak test e) Inadequate bowel preparation f) Anastomosis location greater than 15 cm from the anal verge g) Other intra-operative risks that preclude the subject from undergoing the procedure with the investigational device

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Schedule of Events

The study events and procedures by visit are provided in the tables below.

Pre-operative and Intra-operative Procedures

Procedure	Pre-Operative - 30 to -1 Days	Surgery Day 0
Informed Consent Signed	X	
Pregnancy Test for Female Subjects per hospital policies	X	
Screening/Preliminary Eligibility Determination	X	
Medical History, Concomitant Medications and Physical Examination	X	
ECOG Performance Status assessment	X	
Colorectal Resection Procedure (Index Surgery)		X
Surgery eCRF		X
Concomitant Medications	X	X
Adverse Events, Device Deficiency		X
Colovac 2 Device Implantation Procedure		X
Implantation Usability Questionnaire		X
Colovac 2 Device Position X-ray		X

Schedule of Study Procedures Day 1 - 10

Procedure	Hospital Day 1- 8 Daily	Hospital Day 9 (+3 days)	Hospital Day 10 (-1/+2 days)	If/when applicable
Device Position X-ray	X ¹	X ¹		
Daily Clinical Evaluation	X	X		
CRP	X ²	X ²	X ²	X ²
WBC	X ²	X ²	X ²	X ²
Daily Study Evaluation and Staff Ease of Device Use	X	X		
Trim Sheath (optional)	Day 2 only			
Double Contrast CT Scan of Anastomosis		X		
Concomitant Medications	X	X	X	X
AEs	X	X	X	X
Subject Tolerance and Ease of Use of Device			X	
Endoscopic Evaluation of Anastomosis (BBPS score) with still images			X ³	
Colovac 2 Retrieval			X	
Endoscopic Exam of Mucosa at the anchoring site Post-retrieval with video			X	
Evaluation of Anastomosis Post-retrieval			X	
Conversion to Ostomy				X
Retrieval eCRF			X	
Retrieval Usability Questionnaire			X	

¹ A baseline x-ray documenting device position will be obtained on Day 0 or Day 1. Additional x-rays documenting device position are required if device migration is suspected; otherwise, they are optional.

² Starting on Day 1 or 2, CRP and WBC will be tested every day during hospitalization.

³ If device is removed due to peritonitis and endoscopic evaluation cannot be performed prior to device removal because subject requires emergent surgery, the clinician will determine if the peritonitis is fecal related.

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	Study Procedures for 1 Month Follow-up Visit		
	Procedure	1 Month (±14 days)	If/when applicable
	Endoscopic Exam of Mucosa at the anchoring site with video	X	X
	CRP		X
	WBC	X	X
	Hemoglobin	X	X
	Concomitant Medications	X	
	AEs	X	X
	Conversion to Ostomy		X
	Ostomy Reversal		X

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Anticipated Risks	<p>The risks associated with the use of the Colovac 2 Colorectal Anastomosis Protection Device can be related to the procedure to place the Colovac 2 device, the procedure to remove the Colovac 2 device and to the remaining of the Colovac 2 within the patient's body until sufficient healing of the anastomosis has been achieved.</p> <p><u>Adverse Effects</u></p> <p>All patients will be exposed to the potential risks associated with all medical procedures (including death). Adverse effects that may be caused by or associated with the use of the Colovac Device or the related procedures include, but are not limited to:</p> <p>The general complications of any colorectal surgery.</p> <ul style="list-style-type: none"> a) Pelvic complications <ul style="list-style-type: none"> i Anastomotic bleeding ii Anastomotic stricture iii Anastomotic fistula iv Anastomotic leakage v Anastomosis dehiscence vi Pelvic abscess, collection vii Colonic ischemia viii Peritonitis b) Ileus c) Small Bowel Obstruction d) Incisional Hernia e) Bleeding f) Organ Injury (e.g., bladder, bowel, ureter) g) Nerve Tissue Injury h) Surgical Site Infection i) Prolapse j) Acute Renal Failure k) Sepsis l) AEs associated with potential stoma placement / stoma reversal <p>2) Adverse events that may probably be caused by or associated with the use of the Colovac 2 Device (during and after implant period) include:</p> <ul style="list-style-type: none"> a) Complications from device malfunction that lead to early removal of device and stoma conversion (e.g., migration, stent collapse) such as: <ul style="list-style-type: none"> i Pelvic complications (abscess, collection) ii Anastomosis complications (leakage, fistula, dehiscence) iii Peritonitis iv Sepsis v Colon perforation, obturation or occlusion vi AEs associated with stoma conversion procedure b) Ileus c) Small bowel obstruction d) Colonic ischemia e) Colonic stenosis f) Colon wall damage (e.g., inflammation, hyperplasia, fibrosis, edema, erosion, ulceration) g) Abdominal / Anal pain h) Temporary feces and gas incontinence i) Diarrhea or constipation j) Inflammation of skin around the anus k) Prolapse l) Complication associated with an attempt to reposition the Colovac 2 Device
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	<p>(although Warnings instruct not to re position the Colovac Device)</p> <ul style="list-style-type: none"> m) Complication associated with having to remove the Colovac 2 Device surgically – if endoscopic retrieval is impossible n) Adjacent organ injury due to a broken stent wire poking through the colon o) Additional complications reported for other colorectal stents: <ul style="list-style-type: none"> i Tenesmus ii Fecal impaction iii Bacteremia/fevers iv Foreign body sensation v Intestinal colic (pain not related to operative site) vi Bleeding / blood per anus vii Nausea viii Inability to eat ix Cramping <p>3) Medication side effects, especially anesthesia reactions, including:</p> <ul style="list-style-type: none"> a) Respiratory insufficiencies b) Sedation-induced apnea c) Pneumonia d) Hypotension e) Cardiac arrest (death) f) Nausea and/or vomiting <p>4. Adverse events associated with the stoma:</p> <ul style="list-style-type: none"> a) Skin complications <ul style="list-style-type: none"> i. Peristomal dermatitis ii. Skin irritation iii. Skin breakdown b) Parastomal ulceration c) Parastomal hernia d) Stoma complications: <ul style="list-style-type: none"> i. Stoma necrosis ii. Stoma retraction iii. Stoma prolapse iv. Stoma stenosis e) Dehydration f) Intestinal Obstruction g) Infection h) Sepsis <p>5. Adverse events associated with stoma reversal:</p> <ul style="list-style-type: none"> a) Leakage (at the stoma closure site) b) Surgical Site Infection a) Hernia at stoma site b) Small bowel obstruction c) Ileus (no return of bowel function in 7 days per NSQIP definition) d) Renal failure e) Infection f) Sepsis g) Complications that prevent stoma-closure by 12 Months
Statistical Analysis	All analyses will be defined in a statistical analysis plan (SAP) that will be finalized prior to any knowledge of outcomes or analyses.

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Applicability of OUS Data to US Population and Practice of Medicine	<p>The applicability of the Outside United States (OUS) data to the US population will be assessed by comparing the demographic and baseline characteristics of the OUS subjects to US subjects.</p> <p>The practice of medicine represented by the OUS data will be compared to the practice of medicine in the US.</p>
Ethical Considerations	<p>Institutional Review Board (IRB) or Ethics Committee (EC) approval will be obtained for all sites prior to site initiation.</p> <p>All subjects will sign informed consent prior to enrollment in the study.</p> <p>To protect each subject’s identity, a unique subject identification code will be assigned by the investigator to each subject and used in lieu of the subject’s name on all study documents. Only de-identified, pseudonymized data will be collected.</p> <p>The confidentiality of the identity of subjects enrolled in the study, and the information contained in their data analysis records, will be maintained by the investigators in accordance with local regulatory and IRB/EC requirements.</p>

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3.0 Introduction

3.1 Colorectal surgery

Colon cancer is the second most commonly occurring cancer in women, and the third most commonly occurring cancer in men. There were over 1.9 million new cases worldwide in 2020. Of these 1.9 million cases of cancer in the colon, approximately 500,000 are located in the rectum, the lowest segment of the colon. The majority of patients receives surgical treatment [1]. Colorectal surgery is associated with a high risk of morbidity and mortality in comparison to other general surgery subspecialties. Overall mortality rates following colorectal surgery range from 1 to 16.4%, with morbidity rates as high as 35% [2]. Postoperative complications occur in up to 43% of patients undergoing colorectal procedures [3]. Major postoperative complications include surgical site infection, ileus, bleeding, and anastomotic complications.

The most dreaded complication of this surgery is anastomotic leakage, defined as a communication between the intra- and extraluminal compartments owing to a defect in the integrity of the intestinal wall at the level of the anastomosis. This can result in the rapid development of severe peritonitis, septic shock, and multi-organ dysfunction, and can increase the mortality risk. Protection of the anastomosis with an ostomy may limit the incidence of clinically manifest anastomotic leakage by as much as 30% [4].

3.2 Standard of care ostomy

To minimize the consequences of an anastomotic dehiscence following high-risk colorectal resections, a temporary colostomy or ileostomy (also known as a loop or diverting ostomy) is usually created in order to prevent leakage of fecal content in the abdominal cavity in case of anastomotic complications. Although the anastomosis typically heals within 10 days, ostomy reversal is usually deferred up to 9 months post resection based on the need for adjuvant treatment.

The large majority of patients undergoing low anterior resection of the rectum with Total Mesorectal Excision (TME), which is the standard of care for rectal cancer, typically undergo creation of a temporary ostomy due to the relatively high risk of anastomotic leakage. Known risks for anastomotic leakage include distance of anastomosis location from the anal verge and decreased perfusion of the proximal colon/conduit [5], [6]. The anastomosis itself presents a risk of leak, stricture, and fistula. The anastomotic leak rate is especially high after low anterior resection of rectum, about 10-30%, even when protected with a diverting ostomy [4]. Ileostomies are associated with a significant risk of postoperative complications which can be as high as 43% [3], including dermatologic complications (peristomal skin breakdown), parastomal hernia, stoma necrosis, prolapse or retraction, obstruction and dehydration from high-output. Stoma reversal can cause additional morbidity, including surgical site infection (SSI), anastomotic leakage, bowel perforation, small bowel obstruction, and a 10% risk of hernia at the stoma site. Overall, approximately 20% of stomas are never reversed for a variety of reasons including irreversible anastomotic complications, high surgical risk, and surgeon and patient preference [7].

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Therefore, there is a critical need to develop a device which would protect the anastomosis temporarily, reduce complications while leaving the anastomosis functional for better recovery outcomes, and eliminate the need for ostomies and takedown interventions.

Attempts at developing such devices by using a flexible lining to protect the anastomosis demonstrated proof of concept in terms of improving anastomotic leaks. However, anchoring these devices was a challenge, as the digestive tract is not prone to retaining foreign material at fixed locations. Moreover, an easily reversible anchoring is necessary in order to safely remove the temporary anastomotic protection.

Colovac is a Colorectal Anastomosis Protection device designed to obviate the need for temporary ostomies for patients undergoing colectomy. The device involves the concept of a colorectal bypass and consists of a diverting flexible sheath to protect the anastomosis and of a stent vacuum system which anchors the sheath to the mucosa proximal to the anastomosis.

In light of the above stoma-related complications, there is a critical need to develop an alternative to a diverting stoma such as a protective device that could protect the anastomosis temporarily and reduce the clinical impact of a potential fistula.

The SAFE-2023 Study will evaluate the Colovac 2 System, which includes the Colovac 2 Colorectal Anastomosis Protection Device and the SafeHeal Vacuum Management Device (Smartvac). The Colovac 2 Device includes incremental changes to the Colovac 2 Implant (stent and sheath) and ease of use improvements to the Colovac 2 Introducer. The Colovac 2 System is not yet registered or marketed in any country.

4.0 Investigational device preliminary clinical data

Three prior clinical investigations have been conducted on a Safeheal anastomosis protection device in humans: SAFE-1 Feasibility Study, SAFE-2019 Feasibility Study and the SAFE-2 Pivotal Study.

4.1 SAFE-1 Feasibility Study

The SAFE-1 (NCT03352570) feasibility study on Colovac device enrolled 15 patients in Europe between November 2017 and June 2018. The objective of this SAFE-1 study was to provide a preliminary assessment of performance and safety.

The Colovac device provided effective protection of the anastomosis in 12/15 (80%) subjects during the 14-day post implantation period and allowed avoidance of ostomy creation in 10/15 (67%). Subjects who underwent stoma creation to provide longer-term protection of their anastomosis did not experience any major complications related to the stoma creation procedure. All stoma creation procedures were planned, and none of the subjects required emergency surgery for symptomatic AL.

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The incidence of anastomotic leak (AL) during the Colovac implantation period (0-14 days), was 13%. This rate is equivalent to the average AL rate reported with LAR performed in a similar patient population despite creation of a diverting ostomy (12% to 17 % [3], [4]).

In the SAFE-1 Feasibility Study, the Colovac device provided a safe and minimally invasive alternative to fecal diversion during low anterior resection by protecting the anastomosis during the first 14 postoperative days.

4.2 SAFE-2019 Colovac/Colovac+ Feasibility Study

The SAFE-2019 Study investigated the efficacy, mechanism of action, and safety of the Colovac+ device during the 3-month follow-up period after LAR surgery and implantation of the device. Subjects were analyzed by treatment: 8 subjects with Colovac+ only (PP cohort) and 15 subjects with Colovac+ and VLAS (APP Cohort). The first subject was enrolled in the study on 18 December 2019 and the last patient completed the final follow-up visit on 26 March 2022.

The Colovac+ device resulted in stoma avoidance in 11 of 15 subjects (73%) in the APP cohort (Colovac+ subjects with VLAS) and 5 of 8 (63%) subjects in the 8 Subject cohort (Colovac+ subjects without VLAS), all of whom would otherwise have undergone stoma creation as the standard of care. The other subjects were safely converted to a stoma. The reasons for the four ostomy conversions in the APP cohort were anastomosis stapling failure, anastomotic leakage (incomplete healing), and two prophylactic ostomies for pneumaturia and cardiac rhythm issues. Both prophylactic ostomies were safely reversed by the 3-month follow-up visit.

A clean anastomosis was observed in 87% of the subjects in the APP cohort.

Clinically significant device migration occurred in 2/15 (13.3%) subjects in the APP cohort and any migration occurred in 4/15 (26.6%) subjects. Additionally, there were no reports of complications associated with the device implantation or endoscopic retrieval and no VLAS-related adverse events.

The Colovac device and the VLAS were shown to be safe, and the addition of VLAS resulted in a decrease in DDs, SAEs and migration rates. Additionally, subject tolerance and the technical ease of Colovac implantation and retrieval were acceptable.

4.3 SAFE-2 Colovac+ Pivotal Study

The SAFE-2 Pivotal IDE Study is a multicenter, randomized, controlled trial comparing the safety and effectiveness of the Colovac+ Colorectal Anastomosis Protection Device (Colovac+) used with the VLAS device to diverting ostomy following low anterior resection. The first two subjects at each site were enrolled in a run-arm and implanted with the Colovac+ device. The other subjects were randomized to either the Colovac+ or Control arm of the study.

A total of 15 Colovac+ subjects were enrolled in the run-in arm of the study, 10 subjects were randomized to the Colovac+ arm, and 8 subjects were randomized to the control arm.

One unanticipated adverse device effect occurred when a surgeon attempted to reposition the device immediately upon completion of insertion of the device (even though the IFU specifically warns against

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this), followed by his inability to endoscopically remove the device, which necessitated surgical removal of the device. Upon device removal, the subject was safely converted to a stoma. This is the only event of this nature observed in the 27 cases in this IDE study. Additionally, no events of this nature were observed in the European feasibility studies.

The rate of stoma avoidance was 70% in the Colovac+ randomized arm and 53% in the run-in (training) arm. A clean anastomosis was observed in 92% of all subjects in both Colovac+ arms.

No clinically significant device migration occurred but partial migration occurred in 4/14 (28.6%) of the first 15 Colovac+ subjects enrolled. Clinically significant device migration occurred in 3/12 (25.0%) subjects and any migration (includes clinically significant and partial migration) occurred in 6/12 (50.0%) of the last 12 Colovac+ subjects enrolled; however, only 1/12 (8.3%) of these migrations resulted in stoma creation.

As a higher-than-expected migration rate was observed in the last 12 subjects implanted with the Colovac+ device in the study, enrollment in the study was temporarily suspended while a root cause investigation was conducted. The decision to suspend study enrollment was not related to safety concerns with the device or the study.

The root cause of the migration rate found that the vacuum bottles which is critical to the anchoring of the device, had unpredictable performance. Thus, the enrollment in the study was permanently closed while a Colovac specific vacuum system is developed. As the final follow-up visit (12-month) has not been completed by all subjects, the study is ongoing.

5.0 Investigators and Sites

This study will include up to 50 patients, and will be conducted at 3 sites in Uzbekistan.

6.0 Risk and Benefit Rationale

6.1 Potential benefits

The potential benefits for the patients of Colovac compared to diverting ostomy are:

- Ostomy avoidance by providing temporary protection of the colorectal anastomosis by diverting fecal content through the sheath, reducing direct contact with the anastomosis while maintaining intestinal continuity and function. The potential benefits of ostomy avoidance are:
 - Avoid ostomy procedure related complications
 - Avoid stoma related complications
 - Avoid ostomy reversal procedure related complications
 - Avoid a permanent stoma and related complications
 - Reduce the overall hospital length of stay within 12 months after low anterior resection
 - Provide faster return to full digestive functionality
 - Improve patient Quality of Life (QOL)

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6.2 Anticipated Risks

All patients will be exposed to the potential risks associated with all medical procedures (including death). Potential adverse events include the following:

1. The general complications of any colorectal surgery.
 - a) Pelvic complications
 - i. Anastomotic bleeding
 - ii. Anastomotic stricture
 - iii. Anastomotic fistula
 - iv. Anastomotic leakage
 - v. Anastomosis dehiscence
 - vi. Pelvic abscess, collection
 - vii. Colonic ischemia
 - viii. Peritonitis
 - b) Ileus
 - c) Small bowel obstruction
 - d) Incisional hernia
 - e) Bleeding
 - f) Organ injury (e.g., bladder, bowel, ureter)
 - g) Nerve tissue injury
 - h) Surgical Site Infection
 - i) Prolapse
 - j) Acute renal failure
 - k) Sepsis
 - l) AEs associated with potential stoma placement/stoma reversal
 - m) Death
2. Adverse events that may probably be caused by or associated with the use of the Colovac 2 Device (during and after implant period) include:
 - a) Complications from device malfunction that lead to early removal of device and stoma conversion (e.g., migration, stent collapse) such as:
 - i. Pelvic complications (abscess, collection)
 - ii. Anastomosis complications (leakage, fistula, dehiscence)
 - iii. Peritonitis
 - iv. Sepsis
 - v. Colon perforation, obturation or occlusion
 - vi. AEs associated with stoma conversion procedure
 - b) Ileus
 - c) Small bowel obstruction
 - d) Colonic ischemia
 - e) Colonic stenosis
 - f) Colon wall damage (e.g., inflammation, hyperplasia, fibrosis, edema, erosion, ulceration)
 - g) Abdominal/Anal pain
 - h) Temporary feces and gas incontinence

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-
- i) Diarrhea or constipation
 - j) Inflammation of skin around the anus
 - k) Prolapse
 - l) Complication associated with an attempt to reposition the Colovac 2 Device (although Warnings instruct not to re position the Colovac Device)
 - m) Complication associated with having to remove the Colovac 2 Device surgically – if endoscopic retrieval is impossible
 - n) Adjacent organ injury due to a broken stent wire poking through the colon
 - o) Additional complications reported for other colorectal stents:
 - i. Tenesmus
 - ii. Fecal impaction
 - iii. Bacteremia/fevers
 - iv. Foreign body sensation
 - v. Intestinal colic (pain not related to operative site)
 - vi. Bleeding/blood from anus
 - vii. Nausea
 - viii. Inability to eat
 - ix. Cramping
3. Medication side effects, especially anesthesia reactions, including:
- 1) Respiratory insufficiencies
 - 2) Sedation-induced apnea
 - 3) Pneumonia
 - 4) Hypotension
 - 5) Cardiac arrest (death)
 - 6) Nausea and/or vomiting
4. Adverse events associated with the stoma:
- 1) Skin complications
 - a) Peristomal dermatitis
 - b) Skin irritation
 - c) Skin breakdown
 - 2) Parastomal ulceration
 - 3) Parastomal hernia
 - 4) Stoma complications:
 - a) Stoma necrosis
 - b) Stoma retraction
 - c) Stoma prolapse
 - d) Stoma stenosis
 - 5) Dehydration
 - 6) Intestinal Obstruction
 - 7) Infection
 - 8) Sepsis
5. Adverse events associated with stoma reversal:

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- 1) Leakage (at the stoma closure site)
- 2) Surgical Site Infection
- 3) Hernia at stoma site
- 4) Small bowel obstruction
- 5) Ileus (no return of bowel function in 7 days per NSQIP definition)
- 6) Renal failure
- 7) Infection
- 8) Sepsis
- 9) Complications that prevent stoma-closure by 12 Months

A discussion of the above-mentioned potential adverse events is available in Section 7.2.1 of the Investigator Brochure.

The anticipated risks for the Colovac device will be updated based on the results of this study. The Colovac risks include the risk of a longer hospital stay (up to 10 days, or longer if an ostomy is required).

6.3 Risk to Benefit Rationale

Based on clinical study results of previous versions of the Colovac device, the benefits of the device outweigh the risks. The anticipated risks for the Colovac 2 device will be updated based on the results of this study and a new benefit-risk assessment for the Colovac 2 device will be performed.

7.0 Investigational Device

The Colovac 2 Colorectal Anastomosis Protection Device Instructions For Use are available in Appendix 1.

The Colovac 2 Colorectal Anastomosis Protection System (Colovac 2 System) consists of the Colovac 2 Colorectal Anastomosis Protection Device (Colovac 2 Device) and the Vacuum Management Device (Smartvac). The Colovac 2 Colorectal Anastomosis Protection Device includes the Colovac 2 Implant and the Colovac 2 Introducer (Table 1).

The Colovac 2 Implant is composed of a stent and sheath, and is designed to be used in conjunction with the SafeHeal Smartvac System including canisters with tubing sets.

The Colovac 2 Colorectal Anastomosis Protection Device is a short-term invasive device delivered and positioned through a natural orifice.

Note that Colovac 2 and Colovac may be used interchangeably for the device, implant, introducer, and system.

Table 1: Components of the Colovac 2 System

Component	Part Number
-----------	-------------

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Colovac Colorectal Anastomosis Protection Device	040748
Colovac Device	041463
Introducer	035965
SafeHeal Smartvac	40-0016
SafeHeal Canisters with tubing sets	40-0017

The description hereafter is related to the Colovac 2 device the SAFE-2023 clinical trial. It is a clinical device for investigational use. It is a next generation device based on the original Colovac device (FG-02788-CE) that was CE-marked.

The Colovac 2 device is a sterile, single use disposable device.

7.1 Implant

The Colovac 2 Implant (Figure 1- Bottom) is pre-loaded in the Colovac 2 Introducer (Figure 1 - Top).

Note: The Colovac 2 Implant is designed to be used in conjunction with the SafeHeal Vacuum Management Device.

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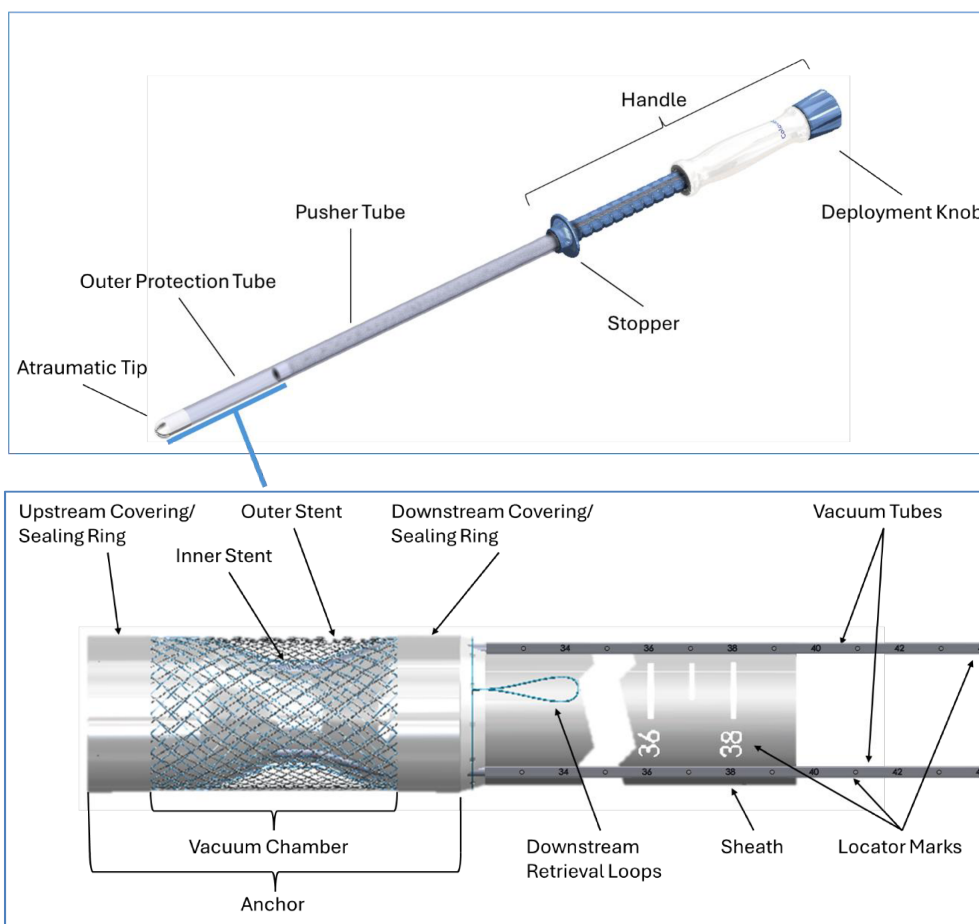


Figure 1: Introducer pre-loaded with the Colovac Device (Top); Colovac Implant (Bottom)

As shown above in Figure 1- Bottom, the Colovac 2 Implant is composed of:

- An anchor consisting of a covered stent assembly delimiting an air- and water-tight volume (i.e., vacuum chamber) in which a vacuum is pulled through two vacuum tubes once the device is correctly deployed in the colon.
- A flexible cylindrical sheath attached to the anchor, covering the anastomosis and with appropriate length so that it protrudes about five centimeters outside the patient's anus. The sheath is an extrusion with a very thin wall, attached with two sealing rings.

Upon contact with the colonic wall, the sealing rings secure a volume (i.e., vacuum chamber) to which a negative pressure is applied over the vacuum tubes. To provide a vacuum distribution all around the anchor, the surface of the sheath material is outfitted with features to ensure circumferential fluidic communication. As a means for monitoring sheath fluctuation and potential migration, the sheath of the Colovac Implant is printed with marks in 1 cm increments.

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There are two tubes that pass through the downstream sealing ring and terminate within the vacuum chamber. These tubes supply vacuum to the vacuum chamber.

The upstream ends of the tubes that are within the vacuum chamber are multiperforated. The unperforated section of the tubes pass through the downstream sealing ring and are long enough to protrude outside of the patient's anus and be attached to the SafeHeal Vacuum Management Device by an off-the-shelf barbed connector. The SafeHeal Vacuum Management Device generates negative pressure in the vacuum chamber. The negative pressure draws the colonic wall toward the mesh of the stent and thus anchors the Colovac Device in place and prevents migration. The reduced diameter of the stent within the vacuum chamber is intended to provide additional mechanical engagement within the colon while vacuum is engaged.

7.2 Introducer

The Colovac 2 Introducer (Figure 1 - Top), is a single use device, which is used to deliver the Colovac Device during a colectomy procedure, once the colorectal anastomosis is complete.

The Introducer consists of two coaxial tubes, specifically, the Outer Protection Tube and the Pusher Tube. Both tubes are linked to each other via a handle.

The Outer Protection Tube is a straight tubular external envelope that holds the anchor element (i.e., stent section) of the Colovac 2 Implant in a compressed state during the insertion procedure. Turning the deployment knob clockwise then releases the stent section of the Colovac Implant from the Introducer into the colon (Figure 2). Once the Colovac Implant has been properly placed at the target site, the Introducer is removed from the colon

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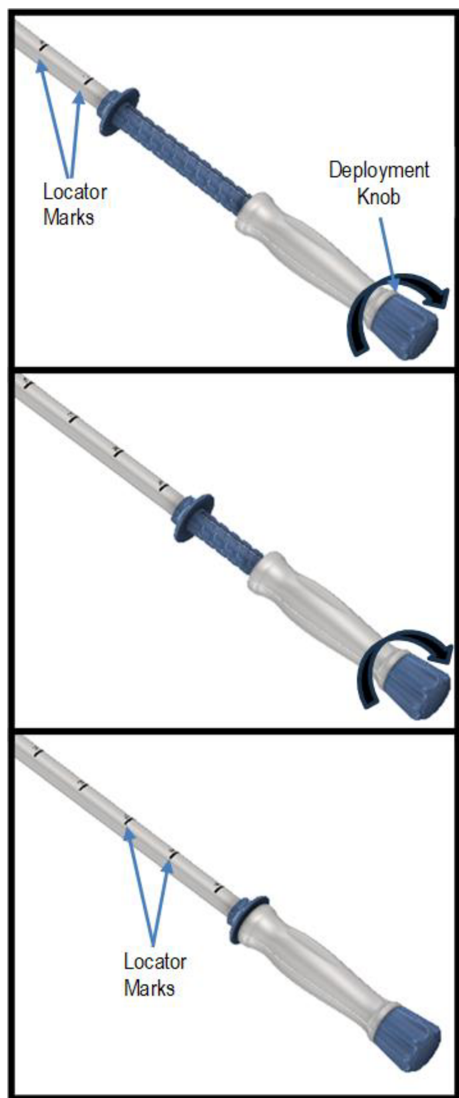


Figure 2: Introducer Handle During Placement of Stent (Top -stent completely inside Introducer; Middle – stent partially deployed; Bottom – stent fully deployed)

The Colovac Colorectal Anastomosis Protection Device is packaged in a sterile pouch fitted in a cardboard box together with the Instructions for Use (IFU).

Vacuum Management Device

The Colovac 2 Device is designed to be used in conjunction with the SafeHeal Vacuum Management Device (**Error! Reference source not found. 3**).

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Figure 3: Vacuum Management Device

The Vacuum Management Device is a single-patient use, non-sterile active device. The device attaches directly to the Colovac 2 Implant and supplies vacuum. It also monitors the vacuum level at the anchoring site, turning on the onboard vacuum pump if the measured vacuum level is outside the pre-determined acceptable range. It provides caregivers with visual and auditory alerts in the event of the following:

- Vacuum Leak detected
- Tubing occlusion detected
- Fluid Collection Cannister full (replacement needed)
- Low Battery (replacement needed)

The housing of the Vacuum Management Device contains several key components, including a vacuum pump (capable of supplying a maximum of -80 kPa), the user interface, the controller printed circuit board, and a battery. The Fluid Collection Cannister interfaces with the housing via a mechanical latching system, creating a seal. An inline filter within the Fluid Collection Cannister protects the vacuum pump. The cannister contains baffling and a fluid absorbent material to absorb any fluids aspirated from the implant. This serves to further protect the vacuum pump.

The vacuum management device is connected to the Colovac device using a tubing set that is supplied with the device.

The System will be indicated for use during patient recovery in hospital/hospital-like environments (e.g., patient hospital rooms).

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7.3 Mechanism of Action

By means of the Introducer, the stent (i.e., anchor) of the Colovac 2 Device is placed in the gastrointestinal (GI) tract lumen, in the transverse neo-colon above the sacral promontory. The flexible sheath which is attached to the anchoring element extends through the colon, covering the GI wall from the anchoring point down to the rectal pouch or just beyond the anal sphincter, thus fully covering the anastomosis and creating a bypass to keep feces and other from communicating with the anastomosis.

By placing the proximal (downstream) part of the stent in the colon above the sacral promontory, the Colovac Device is securely anchored in an intact section of the colon. Any tension that might be applied to the colonic wall by the Colovac Device due to feces passing through will be absorbed by the intact colonic wall, while the anastomosis will not be affected due to the distance between the stent of the Colovac Device and the anastomosis.

The Introducer consists of two coaxial tubes, specifically, the Outer Protection Tube and the Pusher Tube. Both tubes are linked to each other via a handle.

The Colovac 2 Implant is enclosed within the Outer Protection Tube. The upstream tip of the Introducer holds the stent section of the Colovac 2 Implant. The stent is compressed in a radially retracted position for introduction. When compressed, the Colovac 2 Implant has a reduced diameter (16mm) to enable safe insertion and subsequent deployment into the colon. Once released from the Introducer, the stent will expand radially to its uncompressed state against the colonic wall and will thus secure a volume (Vacuum Chamber). As shown below in Figure 4, the Colovac device is designed with a 26.5 mm central stent portion and 37 mm flare at the end, to provide optimal anchoring in the sigmoid colon, which has an average diameter ranging from 30 – 40 mm¹. Furthermore, the colon diameter adapts to the stent diameter.

The Implant is secured to the colon through the continuous application of a negative pressure, which is generated by the SafeHeal Vacuum Management Device. Vacuum is applied to the Colovac Implant when the ends of the tubes extending from the anus are connected to the tube set attached to the Vacuum Management Device. The resulting negative pressure inside the Vacuum Chamber achieves an anchoring effect by drawing the colon wall to the stent. The controlled anchoring is fully reversible without creating significant damage to the colon. The length of the sheath is such that the sheath covers the anastomosis from the anchoring position to beyond the anal sphincter.,. Refer to the IFU for more details.

The healthy colon tissue in which the Colovac Device is placed has sufficient elasticity to allow colons with smaller diameters to expand without injury to accommodate the device, while the device's negative pressure vacuum pulls colons with larger diameters to the stent wall, allowing the device to anchor securely to the colon.

¹ Atlas of Colonoscopy. Francesco Paolo Rossini, Department of Gastroenterology Ospedale Maggiore Torino Italy.

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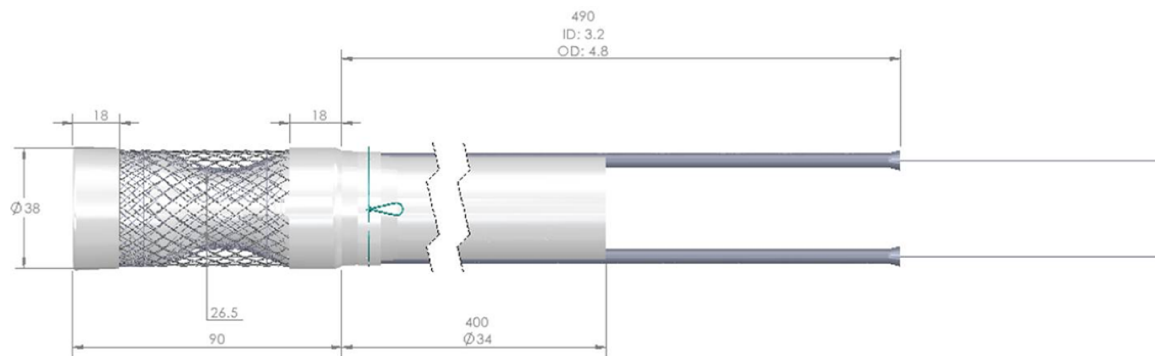


Figure 4: Colovac Implant Dimensions

To prevent accidental displacement of the Colovac 2 Implant by accidental pulling on the patient-external section of the vacuum tubes, the external sections of the vacuum tubes may be fixed to the patient's skin by adhesive strips.

8.0 Intended Use

The SafeHeal Colovac 2 Colorectal Anastomosis Protection Device is intended for use in patients requiring low anterior rectal anastomoses to limit stoma creation to only those patients requiring more time for anastomosis healing when the device is removed, allowing patients with a healed anastomosis to avoid stoma creation.

9.0 Study Design

This is a prospective, open-label, single arm study that will enroll up to 50 patients.

9.1 Study Objective:

The objective of the study is to assess the preliminary, safety and performance of the Colovac 2 System.

9.2 Expected date of the clinical investigation initiation

The first subject was enrolled in the clinical study on July 31, 2024.

9.3 Estimated date of the clinical investigation completion

The site is expected to enroll approximately 5 patients each month. Enrollment and follow-up are expected to take approximately 6 weeks to complete per patient.

9.4 Primary Objective

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The primary study objective is to evaluate the clinically significant (CS) migration rate of the Colovac 2 device during its 10-day implantation period.

9.5 Primary Performance Endpoint at Day 10

The primary performance endpoint is the clinically significant migration rate of the Colovac 2 device during its 10-day implantation period.

Clinically significant migration is defined as movement of device that allows fecal contents to reach the anastomosis site evidenced by:

- Migration of entire stent to or below the Sacral Promontory as indicated by fluctuation in the length of the sheath that extends out of the anus and confirmed by radiographic displacement, with or without subject symptoms or clinical findings suggestive of anastomotic leak (pain, fever, elevated CRP, elevated WBC); or
- Expulsion of the device.

9.6 Secondary Objectives:

The secondary objectives of this study are to assess the:

- Preliminary safety and performance of the Colovac 2 System
- Ease of use of the Colovac 2 Colorectal Anastomosis Protection Device
- Ease of use of the Colovac 2 Introducer and Implant and Vacuum Management Device

9.7 Other Performance Endpoints at Day 10

The other performance endpoints are:

- Ostomy avoidance rate
- Cleanliness of colon immediately prior to device retrieval
- Staff Ease of Use of Device
- Subject Tolerance and Ease of Use of Device

9.8 Safety Endpoints at Day 10

The safety endpoints are:

- Mucosal appearance at anchoring site after device removal
- Device related complications
- All complications

9.9 Measurement Methodology

All patient clinical data will be collected on standardized case report forms.

Safety will be evaluated by determining the incidence of intra- and post-surgical complications and adverse events (including spontaneous patient reports) after 10 days and 4 weeks. Complications and adverse events will be recorded on the case report forms.

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9.10 Primary Analysis Population

Patients treated with the Colovac 2 Colorectal Anastomosis Protection Device will be included in the intent to treat (ITT) population. Patients who withdraw consent prior to enrollment or who do not meet the eligibility requirements (per the inclusion and exclusion criteria) prior to enrollment will be recorded on a screening log but will not be included in any analyses. Subjects who are enrolled and excluded from the study due to adverse events prior to implantation with the Colovac 2 Colorectal Anastomosis Protection Device will not be included in the ITT population.

9.11 Physician Training

All physicians included in this clinical trial are skilled in colorectal surgery. All treating physicians will have been trained on the use of the Colovac 2 Device prior to treating the first enrolled patient, as per internal SafeHeal training procedures and Investigator training plan specifications. The Site Initiation Visit will include a review of relevant procedural workflow and instructions for use for the SafeHeal Colovac 2 Colorectal Anastomosis Protection Device.

9.12 Patient Recruitment

Patients who meet eligibility criteria and agree to participate will be consented and enrolled. Upon regulatory and ethics committee approval of this protocol, patient enrollment will begin.

10.0 Patient Selection

10.1 Patient Selection Criteria for Eligibility

Inclusion Criteria:

Candidates for this study must meet ALL of the following criteria:

1. Adult patients (18 years of age or older)
2. Eligible to undergo open or minimally invasive sphincter-sparing low anterior resection with planned diverting loop ileostomy for malignancy, based on multidisciplinary team recommendations
3. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2
4. Willingness to comply with protocol-specific treatment and study visits and to sign a written Informed Consent Form

Exclusion Criteria:

Candidates will be excluded from the study if ANY of the following conditions apply:

Preoperative

1. History of left sided colitis
2. Known allergy to nickel or other components of the Colovac 2 System
3. Pregnant or nursing female subject

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4. Concomitant major surgical procedure in combination with Colorectal resection (i.e., hepatectomy)
5. Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation, impair the ability of the participant to undergo protocol described procedures or interfere with the interpretation of study results including, but not limited to:
 - a) Stage IV colorectal cancer unless curative intent R0 resection is planned AND there is no associated peritoneal disease
 - b) Immunodeficiency (CD4+ count < 500 CU MM)
 - c) Systemic steroid therapy within the past 6 months
 - d) Systemic infection at the time of surgery or requiring systemic antimicrobial therapy up to 1 week before surgery
 - e) Major surgical or interventional procedures within 30 days prior to this study or planned surgical or interventional procedures within 30 days of entry into this study
 - f) Diagnosis of bowel obstruction, bowel strangulation, peritonitis, bowel perforation, intraabdominal infection, ischemic bowel, carcinomatosis
 - g) Fecal incontinence, involvement of sphincter by the neoplastic disease or evidence of extensive local disease in the pelvis seen on pre-operative imaging
 - h) Severe malnutrition which is defined as at least 10% weight loss within 3 months prior to enrollment.
6. The subject is currently participating in another investigational drug or device study

Intraoperative

7. Anastomosis placement above the sacral promontory
8. Occurrence of any of the following during the colorectal surgery:
 - a) Blood loss (>750 cc)
 - b) Blood transfusion
 - c) Any new sign of ischemia
 - d) Positive air leak test
 - e) Inadequate bowel preparation
 - f) Anastomosis location greater than 15 cm from the anal verge
 - g) Other intra-operative risks that preclude the subject from undergoing the procedure with the investigational device

10.2 Expected enrollment rate / screening results

The clinical site is expected to enroll approximately 5 patients each month.

10.3 Screening Procedures

All patients considered for colorectal surgery and eligible for enrollment as determined by the study investigator should have the study explained to them, be given the study information sheet and informed consent form, and allowed time to consider whether or not they wish to take part in the study. The Investigator or a member of his/her staff should inform the patient about the study's

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purpose and risks/benefits. If the patient agrees to take part in the study and signs the consent form, the patient can then be screened by the investigator for study eligibility. If all inclusion criteria and no exclusion criteria are met, the patients should be enrolled in the study. Patients who give consent to take part in the study and subsequently do not meet the eligibility criteria will not be included in the intention to treat (ITT) population as detailed in 8.1.

10.4 Informed Consent

The Investigator or his/her staff will approach the patient to obtain written informed consent. The background of the proposed study and the potential benefits and risks of the study should be explained to the patient. Sufficient time will be given to the patient to understand the information provided and to ask any question related to the study and/or to the investigational device to the investigator and understand the answer provided.

The patient must sign the consent form prior to any evaluation specifically required for the study outside of routine practice. Failure to provide informed consent renders the patient ineligible for the study.

This form or a modification of it must have approval of the study site's Ethics Committee prior to obtaining patient consent. Patients may not be consented after receiving any medication that might alter their ability to comprehend the consent form (e.g., sedatives, narcotics, etc.).

The process of consent must be documented in the patient's hospital file.

11.0 Description of Treatments and Procedures

A summary of the study procedures by visit is provided in the tables below.

The pre-operative and intra-operative procedures are summarized below in Table 2.

Table 2: Pre-operative and Intra-operative Study Procedures

Procedure	Pre-Operative - 30 to -1 Days	Surgery Day 0
Informed Consent Signed	X	
Pregnancy Test for Female Subjects per hospital policies	X	
Screening/Preliminary Eligibility Determination	X	
Medical History, Concomitant Medications and Physical Examination	X	
ECOG performance status assessment	X	
Colorectal Resection Procedure (Index Surgery)		X
Surgery eCRF		X
Concomitant Medications		X

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Procedure	Pre-Operative - 30 to -1 Days	Surgery Day 0
Adverse Events		X
Colovac 2 Device Implantation Procedure		X
Implantation Usability Questionnaire		X
Colovac 2 Device Position X-ray		X

The procedures for Days 1 – 10 after surgery are summarized below in Table 3.

Table 3: Study Procedures for Days 1 - 10

Procedure	Hospital Day 1- 8 Daily	Hospital Day 9 (+3 days)	Hospital Day 10 (-1/+2 days)	If/when applicable
Device Position X-ray	X ¹	X ¹		
Daily Clinical Evaluation	X	X		
CRP	X ²	X ²	X ²	X ²
WBC	X ²	X ²	X ²	X ²
Daily Study Evaluation and Staff Ease of Device Use	X	X		
Trim Sheath (optional)	Day 2 only			
Double Contrast CT Scan of Anastomosis		X		
Concomitant Medications	X	X	X	X
AEs	X	X	X	X
Subject Tolerance and Ease of Use of Device			X	
Endoscopic Evaluation of Anastomosis (BBPS score) with still images			X ³	
Colovac 2 Retrieval			X	
Endoscopic Exam of Mucosa at the anchoring site Post-retrieval with video			X	
Evaluation of Anastomosis Post-retrieval			X	
Conversion to Ostomy				X
Retrieval eCRF			X	
Retrieval Usability Questionnaire			X	

¹ A baseline x-ray documenting device position will be obtained on Day 0 or Day 1. Additional x-rays documenting device position are required if device migration is suspected; otherwise, they are optional.

² Starting on Day 1 or 2, CRP and WBC will be tested every day during hospitalization.

³ If device is removed emergently due to peritonitis and endoscopic evaluation cannot be performed prior to device removal, the clinician will determine if the peritonitis is fecal related.

The procedures for the 1-month follow-up visit are summarized below in Table 4.

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Table 4: Study Procedures for 1-Month Follow-up Visit

Procedure	1 Month (30±14 days)	If/when applicable
Endoscopic Exam of Mucosa at the anchoring site with video	X	X
CRP		X
WBC	X	X
Hemoglobin	X	X
Concomitant Medications	X	
AEs	X	X
Conversion to Ostomy		X
Ostomy Reversal		X

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11.1 Pre-operative Evaluation

Prior to the start of the study, the following steps will be completed and documented in the Case Report Form (CRF):

1. Confirmation that all inclusion criteria are passed, as defined in section 10.1.
2. Confirmation that no exclusion criteria are present, as defined in section 10.1.
3. Signed informed consent is obtained.
4. Within two weeks prior to the study unless otherwise noted, all patients enrolled into this study will undergo and have documented the medical history and ECOG evaluation, and physical examination. Additionally, concomitant medications will be documented.

11.2 Equipment

Each investigational site will provide standard colorectal surgery equipment for performing the Study and procedure.

SafeHeal will provide the following equipment:

- Colovac 2 Colorectal Anastomosis Protection Device pre-loaded inside its Introducer for each procedure, with back up
- SafeHeal Smartvac System
- SafeHeal canisters with tubing sets

Please refer to both the Instructions for Use for the Colovac 2 device and the Instructions for Use for the SafeHeal Vacuum System.

11.3 Study Procedures

D0 - Surgery and device implantation

The colorectal surgery is performed according to standard of care. After tumor resection and anastomosis creation, the device is implanted according to the procedure described in the Instructions for use.

Particular attention shall be paid to device positioning and to the Smartvac system connection.

D2 - Sheath cutting (optional)

At D2, the sheath may be cut according to the procedure described in the Instructions for use.

D0 – D10 (-1/+2) - Patient monitoring

The patient will be monitored daily until the device is retrieved on Day 10.

Patient Daily monitoring includes:

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- Fever
- Pulse
- Abdominal exam

Device daily monitoring should occur twice a day (T1 morning and T2 evening) and includes:

- Presence of fluid in the vacuum system collection reservoir
- Absence of blockage on the vacuum tube
- Length of the sheath protruding from the anus

If the stent migrates below the sacral promontory, documented by an X-ray or computed tomography, the physician should consider converting the patient to the standard of care ostomy within 24 hours.

Monitoring of C-reactive protein (CRP) and white blood cell (WBC) levels:

Starting on Day 1 or 2, CRP and WBC shall be tested every day during hospitalization.

Staff Ease of Use of Device:

The Staff member performing the Device daily monitoring will complete the Staff Ease of Use of the Device Questionnaire.

Day 9 (+3 days)

The day before device retrieval, a double contrast CT-scan shall be obtained to evaluate anastomosis integrity and healing. Images will be recorded and uploaded to a secure server, and read by an independent reviewer (CEC) to determine presence or absence of a leak and the description of the leak (if applicable).

Device retrieval D10 (-1/+2 days)

The device retrieval is composed of the following sequence:

1. Colonoscopy will be performed prior to the device retrieval, between the colon wall and the sheath, to assess visually the presence of feces (sealing function integrity of the Colovac 2 device) and the integrity of the anastomosis. The Boston Bowel Preparation Scale (BBPS, see Appendix 2) score will be assessed by an independent reviewer (CEC). Still images of the anastomosis will be captured during the procedure and the pseudonymized images should be sent on a secure platform for analysis, and anastomosis healing and signs of leak will be assessed by an independent reviewer (CEC).
2. Device retrieval - Please refer to the Instructions for use of the Colovac 2 Device for retrieval instructions.
3. Endoscopic evaluation after device retrieval

An endoscopic evaluation with video will be performed immediately after retrieval of the Colovac 2 Device to check for colonic wall injury at the anchoring site and to evaluate anastomotic integrity. The pseudonymized imaging should be uploaded on a secure platform for analysis. These will be

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analyzed by an independent reviewer (CEC) to determine vessel impact, with an assessment of mucosal appearance by grading bleeding, perforation and ulceration. If ulceration is present, percentage of ulceration will also be assessed.

After retrieval of the Colovac 2 Device, the anastomosis will be evaluated.

If an anastomotic defect is identified, treatment will be at the surgeon's discretion. Anastomotic defects/leaks may be treated with antibiotics only, and/or by percutaneous drainage, and/or surgically (revision of the anastomosis, repair of the anastomotic defect, stoma creation).

Handling of anastomotic complications during the implantation period

Any subject presenting with clinical signs suggestive of anastomotic leakage observed during the implantation period of the Colovac 2 Device will be treated as per standard clinical practice.

Subjects with clinical signs or symptoms of anastomotic leakage will undergo CT scan. Definitive treatment of anastomotic leakage will be per the treating surgeon's discretion and based on the severity of the clinical symptoms and radiological findings. Treatment may consist of antibiotics only, and/or percutaneous drainage, and/or reoperation.

11.4 Patient Follow-up

At 1-month post index surgery (± 14 days) an endoscopic evaluation with video should be performed to assess the healing of the colon mucosa at the anchoring site. The pseudonymized video should be uploaded on a secure platform for analysis. This video will be analyzed by an independent reviewer (CEC) to determine vessel impact, with an assessment of mucosal appearance by grading bleeding, perforation and ulceration. If ulceration is present, percentage of ulceration will also be assessed.

The 1-month visit will also collect any concomitant medications that have been added or removed and adverse events that have occurred since the Day 10 visit. Additionally, white blood count, hemoglobin and ostomy status will be collected.

11.5 Withdrawal Criteria

Subjects will be withdrawn from the clinical investigation for any of the following reasons:

1. Subject requests early discontinuation.
2. Subject is lost to follow up.

The subject can leave the investigation at any time, at the subject's request. The reason for withdrawal will be investigated and carefully documented in the subject's medical records and the appropriate section of the case report form. When a subject withdraws or is withdrawn from the clinical investigation, a final evaluation/follow up will be performed as completely as possible.

11.6 Missed Follow-up/Lost to Follow-up

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At least three attempted contacts shall be made. In addition, the general practitioner shall be contacted and if still no news, a pre-defined contact person as per informed consent shall be contacted prior to documenting the missed follow up. When the subject cannot be contacted and no information can be obtained in another way (from either the subject's general practitioner or subject's family), the civil registry should be contacted to verify whether the subject is still alive.

For each missed or lost to follow up a clinical investigation plan deviation form must be completed clearly documenting the attempts to reach the subject for a given visit

12.0 Investigational Device Management

12.1 Packaging and labeling

The Colovac 2 device possesses a label that states: "Exclusively for Clinical Investigations" and "CAUTION - Investigational device. Limited by United States law to investigational use."

All labels include a fixed information section (to include the product name, Legal Manufacturer name, storage conditions, instructions) and variable information section (Lot Number, expiry date).

12.2 Distribution and shipment

Distribution and shipment of product is managed by SafeHeal and CRO according to procedures described in the device management plan. Each shipment of device supplied for the study will contain a shipment delivery note to assist in maintaining current and accurate inventory records. When a shipment is received, the site will acknowledge receipt.

12.3 Device Storage

The device should be examined immediately upon arrival at the study site. If the supplied device appears to be damaged or have reached the expiration date, the sponsor should be contacted immediately, and another product utilized for the implantation procedure.

Devices must be kept in a secure, limited-access storage area. Sites will ensure that only authorized site personnel will have access to study devices.

12.4 Device Accountability

SafeHeal and the CRO are responsible for managing the device supply and tracking and will follow study specific device accountability procedures for the Colovac 2 device.

The dedicated Device Accountability Log will be maintained and kept up to date at all times. The identification number of the subject, the date used, lot number, expiry date of the study device implanted, and the date and quality of study devices returned will be recorded.

Accountability of the received devices including their disposition (implanted, deficiency, and unused) study devices, will be performed and recorded on the proper study Device Accountability Log.

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12.5 Device return

Before any use of a device, the expiry date has to be checked. In case of expiry, the device will be returned to the Sponsor according to the device management plan.

All used Colovac devices and any device with a device deficiency will be returned to the device legal manufacturer (SafeHeal) for analysis in the biohazard boxes provided with relevant CRFs pages for deficiency.

All study devices not used during implantation will be returned to the Sponsor as described in the device management plan.

13.0 Data Analysis and Acceptance

Data will be managed according to the Data Management Plan and analyzed following the Statistical Analysis Plan (SAP).

All study results will be analyzed using widely accepted statistical or graphical software. Patient data listings and tabular and graphical presentations of baseline and operative characteristics and outcome results will be provided. Presentation of summary statistics for continuous variables such as age will include standard descriptive statistics including, mean, and standard deviation, as well as the minimum and maximum values. For categorical variables, e.g., gender, the number, and percent of patients in each category will be calculated. Confidence intervals for primary and secondary outcomes will be presented and will be two-sided unless otherwise stated, employing a significance level of 0.05.

Additionally, all adverse events will be summarized by type of event, severity, relationship to the device and/or procedure, and timing of event relative to the procedure date.

Safety of the subjects participating in this clinical investigation will be monitored throughout the clinical investigation using the Adverse Event reporting process in the EDC system/paper CRF, to identify actual and potential safety issues.

Adverse events will be reported according to the definitions of ISO 14155:2020 and the requirements of MDCG 2020-10-1, while recognizing and following the requirements including reporting timelines specified in other specific laws, regulations, standards and/or guidelines as appropriate and as required by the countries in which the study is conducted.

14.0 Safety

14.1 Device Deficiency

According to ISO14155:2020, the definition of a device deficiency is:

Any inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. Device deficiencies include malfunctions, use errors, and

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inadequacy in the information supplied by the manufacturer including labeling. This definition includes device deficiencies related to the investigational medical device or the comparator.

All investigational device deficiencies will be documented in the eCRF. Devices that undergo such deficiency will be returned to the device legal manufacturer (SafeHeal) for analysis in the biohazard boxes provided with relevant CRFs for deficiency.

Recall can be triggered by Legal Manufacturer based on complaint analysis or by FDA or National Competent Authorities decision. According to sponsor internal procedure, immediate identification of devices and location are given by a specific tracker managed by the sponsor. Recall actions and recording follows internal sponsor procedure.

The above-mentioned devices must be returned to SafeHeal after appropriate decontamination per hospital guidelines.

The Sponsor and the Investigators will use the following definition to determine if a device deficiency could have led to a serious adverse event.

Device deficiencies that might have led to a serious adverse event

- a) if appropriate action had not been taken,
- b) intervention had not occurred, or
- c) circumstances had been less fortunate,

shall be reported under the same conditions as a serious adverse event. Note: FDA recognizes an earlier version of this global consensus standard (ISO14155:2011).²

Malfunction

According to ISO 14155:2020, the definition of a malfunction is:

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or Clinical Investigation Plan or Investigator Brochure.

Use Error

According to ISO 14155:2020, the definition of a use error is:

User action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user

Note 1: Use error includes the inability of the user to complete a task.

Note 2: Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment.

² <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/detail.cfm?standard=identification> no=36910

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Note 3: Users might be aware or unaware that a use error has occurred.

Note 4: An unexpected physiological response of the patient is not by itself considered a use error.

Note 5: A malfunction of a medical device that causes an unexpected result is not considered a use error.

14.2 Adverse Events

All Adverse Events will be recorded on the AE eCRF.

Definitions

Adverse Events (AE) per ISO 14155:2020

The definition of an adverse event is:

Any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

Note 1: This definition includes events related to the investigational medical device or the comparator.

Note 2: This definition includes events related to the procedures involved

Note 3: For users or other persons this definition is restricted to events related to the use of the investigational medical devices or comparators.

Serious Adverse Events (SAE) per ISO 14155:2020

The definition of a Serious Adverse Event is:

Any adverse event that led to any of the following:

- a) death,
- b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:
 - 1) a life-threatening illness or injury,
 - 2) a permanent impairment of a body structure or a body function, including chronic disease or
 - 3) in-patient or prolonged hospitalization, or
 - 4) medical or surgical intervention to prevent life threatening illness or injury, or permanent impairment to a body structure or a body function.
- c) fetal distress, fetal death or a congenital abnormality, or birth defect including physical or mental impairment

Note: Planned hospitalization for a preexisting condition, or a procedure required by the CIP without serious deterioration in health is not considered as a serious adverse event.

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Unanticipated Adverse Device Effect (UADE) per 21CFR 812.3(s)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Adverse Device Effect (ADE) per ISO 14155:2020

An adverse event related to the use of an investigational medical device.

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Note 3: This includes 'comparator' if the comparator is a medical device.

Serious Adverse Device Effect (SADE) per ISO 14155:2020

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE) per ISO 14155:2020

A serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment.

Note 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, or severity or outcome has been identified in the risk assessment.

Serious Health Threat per ISO 14155:2020

Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users, or other persons, and that requires prompt remedial action for other subjects, users or other persons.

Note 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

AE Reporting

All the adverse events identified by the physician or the patient during the study must be reported as soon as possible on the AE eCRF, regardless of classification, seriousness, severity, outcome, or

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causality. Additional documentation may be requested by the Sponsor including, but not limited to, a written subject narrative detailing the clinical course of the AE.

All AEs must be documented in the in the Adverse Event eCRF including:

- Description of the event
- Date of onset
- Relationship to the LAR procedure (index surgery), investigational Colovac device (including implantation and removal procedures), SmartVac System, Canisters with tubing sets, and stoma (including creation and reversal procedures).

For the purpose of harmonizing reports, each AE will be classified according to four different levels of relationship (causality):

1. Not related
2. Possible
3. Probable
4. Causal (Definite) relationship

The sponsor and the investigators will use the following definitions to assess the relationship of the AE to the Colovac device, the SmartVac System, canisters with tubing sets, stoma, the LAR surgical procedure, Colovac insertion/retrieval procedure, and stoma placement/retrieval procedure.

Not related	<p>Relationship to the device or procedures can be excluded when:</p> <ul style="list-style-type: none">• the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device• the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is• previously known) and is biologically implausible;• the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible -• and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;• the event involves a body-site or an organ that cannot be affected by the device or procedure;• the serious adverse event can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect• of another device, drug, treatment or other risk factors);• the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; <p>In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.</p>
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Possible	The relationship with the use of the investigational device, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug, or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
Causal (Definite) relationship	<p>The serious adverse event is associated with the investigational device, or with procedures beyond reasonable doubt when:</p> <ul style="list-style-type: none"> the event is a known side effect of the product category the device belongs to or of similar devices and procedures; the event has a temporal relationship with investigational device use/application or procedures; the event involves a body-site or organ that <ul style="list-style-type: none"> the investigational device or procedures are applied to; the investigational device or procedures have an effect on; the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known); the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible); other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; harm to the subject is due to error in use; -the event depends on a false result given by the investigational device used for diagnosis, when applicable

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

Severity of the AE will be assessed using the following:

- Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: minimal, local, or noninvasive intervention indicated; limiting
- Severe: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling
- Life-threatening: urgent intervention indicated, disabling
- Fatal: death related to AE

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In addition, the severity of the event will be assessed using the Clavien-Dindo classification³ shown in Table 5.

Table 5: Clavien-Dindo Classification of Severity

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anesthesia
- IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
- IVa	Single organ dysfunction (including dialysis
- IVb	Multi organ dysfunction
Grade V	Death of a patient

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

The following information will also be collected:

- Seriousness using the SAE definition above
- Action taken
- Date of resolution
- Outcome

³ Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-213.
doi:10.1097/01.sla.0000133083.54934.ae

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All AEs (regardless of relationship) must be collected from the time the informed consent is signed through the last follow-up visit. All AEs must be recorded on the appropriate AE eCRF and in source documents.

All adverse events will be followed until the event is resolved or stabilized and/or deemed permanent, or until the subject's participation in the study ends.

If the AE meets the criteria for an SAE, the investigator must complete the AE form in the EDC system, as soon as possible, but no later than 3 days of knowledge of the event.

In addition, anastomotic leaks will be graded according to the ISREC grading system that classifies ALs into one of three grades based on severity and required treatment (see appendix 3).

An independent Clinical Evaluation Committee (CEC) will be responsible for adjudicating the severity, seriousness, and relatedness of the adverse events as defined in the CEC Charter. The adjudication decision of the CEC is the final event decision and the one which will be used for the AE analyses. The CEC responsibilities are discussed in the CEC Charter.

14.3 Clinical Events Committee

An independent CEC will operate under a charter that documents the process for adjudication of data for this study. The CEC will consist of a minimum of three (3) non-SafeHeal employed physicians that are not participating investigators for the study, including a CEC chairperson. Other than receiving compensation from the sponsor for their time spent as CEC members, CEC members should have no other relationship with the CRO, sponsor or investigator that could impair the members' ability to objectively review study data.

The CEC will conduct a medical review at regular intervals according to the CEC Charter. The CEC is responsible for reviewing data extracted from the clinical database, reviewing applicable definitions, and determining final classifications for adjudication parameters.

The CEC will assess the serious adverse events, adverse device effects, anastomosis leaks, index surgery related or ostomy related AEs with Clavien Dindo severity III-V or II and re-admission to hospital, BBPS and anastomosis healing, and mucosal appearance at anchoring site, according to the CEC Charter and this protocol.

14.4 Suspension or premature termination

If the Sponsor determines that the study presents an unacceptable risk, the study may be terminated. Termination shall occur not later than 5 working days after the sponsor makes this determination. SafeHeal will notify all participating investigators, Ethics Committees, and the appropriate regulatory authorities of the termination of the investigation.

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15.0 Data Handling

15.1 Data Collection

Study data will be collected on electronic Case Report Forms (eCRF) utilizing an electronic data collection system (EDC) that complies with the relevant international regulations and standards and provides the capability of performing major data management within a consistent, auditable, and integrated electronic environment (query management, data entry, data validation). The investigators and study site staff will be supplied with the necessary documentation before using the system and support will be provided by the study monitors and the eCRF help-desk system, as needed. Specific details of data review, database cleaning and data querying will be described in a separate Data Management Plan (DMP).

The Investigator shall maintain information in the subject's medical records that corroborates data collected on the eCRFs. Subject data entered onto the eCRF will be compared to information originally recorded on source documents (i.e., medical records, professional notes, laboratory reports, investigation-specific worksheets, etc.). Sponsor or designee will provide clinical monitoring as specified in Section 16.3.

15.2 Data confidentiality and protection

The patient identification list is under strict control of the Investigator/Principal Investigator and will not be transferred outside of the hospital. Data recorded by eCRF shall be pseudonymized to comply with the applicable data security and protection rules (General Data Protection Regulation -GDPR). The Sponsor shall take all necessary measures to prevent unauthorized access to their computers and ensure that no data is lost. Only study personnel directly involved in the conduct of the trial will have authorization to enter or access data in the clinical trial database. There will be a complete audit trail of all data access.

Any source documentation (procedure reports, imaging studies, lab reports, death certificates, etc.) that is sent to the sponsor, reviewing committees, or the core lab, should have all subject identifiers removed and replaced with the subject number.

Subject confidentiality and privacy are strictly held in trust by the participating investigators, their staff, the sponsor(s) and their representatives. This confidentiality is extended to cover all testing performed in addition to the clinical information relating to subjects. Therefore, the trial protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the trial, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The trial monitor, other authorized representatives of the sponsor, representatives of the IEC, and regulatory agencies may inspect all documents and records required to be maintained by the

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investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this trial. The clinical trial site will permit access to such records.

The trial subject's contact information will be securely stored at each clinical site for internal use during the trial. At the end of the trial, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IEC, Institutional policies, or sponsor requirements.

Trial subject research data, which is for the purposes of statistical analysis and scientific reporting, will be transmitted to and stored by the Sponsor or their designee. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique trial identification number. The trial data entry and trial management systems used by clinical sites and by the Sponsor research staff will be secured and password protected. At the end of the trial, all trial databases will be de-identified and archived.

15.3 Deviations

A protocol deviation is defined as any instance during the conduct of the study in which the investigator or other site personnel changed or failed to adhere to the study design or procedures specified by the protocol. Investigative sites are expected to comply with the study protocol except where necessary to protect the life or physical well-being of a subject in cases of medical emergency,

Throughout the conduct of the study, data will be reviewed by Sponsor for the presence of deviations. Study personnel will report any deviation from the study protocol or regulation upon occurrence. Sponsor monitors will also review data and conduct for any deviations during on-site visits per the monitoring plan.

15.4 Data storage/archives

The investigators must maintain adequate and accurate records to document the conduct of the clinical study and to substantiate the clinical study data. These records include regulatory documents as required by applicable regulations, and the subjects' source documents, clinical trial progress records, laboratory reports, electronic case report forms, signed informed consent forms, device accountability records, correspondence with the EC and clinical trial monitor or sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical trial/investigation.

Regulatory documents are those documents that individually and collectively permit evaluation of study compliance with applicable regulations and evaluation of the quality of the data produced.

These documents will be filed in an Investigator Site File provided by the Sponsor or designee. This file shall be used to facilitate and ensure filing of all relevant regulatory documents during and after the study. The investigator will be responsible for keeping the Investigator Site File updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

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The investigator shall arrange for the retention of all study documents and records, including subject records, eCRFs, device inventory/accountability log, signed informed consent forms and the patient identification list for at least 15 years, or as per local regulatory requirements, after completion or discontinuation of the study.

16.0 Regulatory Responsibilities

16.1 Investigator Responsibilities

The Principal Investigator is responsible for ensuring the investigation is conducted according to the CIP and all signed agreements by the investigative team. The Investigator is not allowed to deviate from the CIP. This section describes these responsibilities at his/her site. Also, the Principal Investigator and participating sites must complete and sign the Clinical Trials Agreement contract, and the Principal Investigator must complete and sign the Investigator Agreement prior to enrollment of the first subject.

The investigator must submit the study protocol to his/her Ethics Committee and obtain their written approval before being allowed to consent a subject in the study. The investigator is also responsible for fulfilling any conditions of approval imposed by the Ethics Committee, such as regular reporting, study timing, etc.

Part of the Ethics Committee approval must include approval of an Informed Consent text specific to the trial. The investigator or staff must administer this approved Informed Consent text to each prospective study patient, and obtain the patient's signature on the text, prior to enrollment in the study.

Informed Consent

Subject participation in this clinical trial is voluntary. Informed Consent is required from each subject. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any procedures, testing or data collection being done specifically for the trial.

The ICF must be in a language understandable to the subject and privacy language shall be included in the body of the form or as a separate form as applicable. Approval from the EC is necessary before the ICF can be used.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations, and guidelines:

- Be conducted by the Principal Investigator or designee authorized to conduct the process
- Include a description of all aspects of the clinical trial that are relevant to the subject's decision to participate throughout the clinical trial
- Avoid any coercion of or undue influence of subjects to participate
- Not waive or appear to waive subject's legal rights

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- Use native language that is non-technical and understandable to the subject or his/her legal representative
- Provide ample time for the subject to consider participation and ask questions if necessary
- Ensure important new information is provided to new and existing subjects throughout the clinical trial

The ICF shall always be signed and personally dated by the subject and by the investigator and/or an authorized designee responsible for conducting the informed consent process.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the informed consent form after the oral consent of the subject is obtained.

The original signed ICF will be retained by the site and a copy of the signed and dated document, and any other written information must be given to the person signing the form. Subjects may withdraw consent at any time throughout the course of the trial.

The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g., use of a translator, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a trial, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/IEC. The new version of the ICF must be approved by the IRB/IEC, who will also determine the subject population to be re-consented.

16.1.1 Records

The Study Team will be comprised of the Principal Investigator (PI), investigators, the study coordinator(s), members of SafeHeal, contractors designated by SafeHeal, or any other staff as prescribed by the PI. The members of the study Team will be documented on a delegation log or study staff log prior to enrollment of the first subject. Amendments after enrollment of the first subject may be made and will be documented by the PI.

The Principal Investigator is responsible for maintaining the following (the responsibilities may be delegated by the Principal Investigator to the Study Coordinator):

- Accurate, complete, and current records relating to the conduct of the study. The data for some of these reports may be available in electronic form but must be made available for monitoring by the Sponsor or monitor.

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- All correspondence with study investigators, an IRB/Ethics Committee, the sponsor, a monitor, or competent authorities, notified bodies or the FDA, including required reports.
- Records of receipt, use, or disposal of the study device, including receipt dates, serial and lot numbers, names of all persons who received or used the device, why and how many devices were returned to the sponsor or otherwise disposed of.
- Records of each subject's case history, including study-required Case Report Forms, evidence of informed consent, all relevant observations of adverse device effects, the condition of each subject upon entering and during the course of the investigation, relevant medical history, the results of all diagnostic testing, and the date of each study treatment.

16.1.2 Reports

The principal investigator shall report all adverse events and device deficiencies in the appropriate sections of the e-CRF and provide where requested by the sponsor, the necessary clinical or technical information that may contribute to clarifying the circumstances.

The principal investigator shall report:

- a) any serious adverse event (SAE) that has a causal relationship with the investigational device, or the investigation procedure or where such causal relationship is reasonably possible.
- b) any device deficiency (DD) that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
- c) any new findings in relation to any event referred to in points a) and b).

to the sponsor immediately, but not later than 3 calendar days after investigation site study personnel's awareness of the event, using the appropriate page of the e-CRF. In case of any eCRF system failure, a paper CRF page may be completed and sent to the sponsor following the same time requirements.

Reporting of adverse events starts from the time point the subject is enrolled in the clinical investigation (i.e., signed informed consent). This means that any adverse events related to or reported during the screening assessments are to be reported.

The principal investigator shall document all adverse events and device deficiencies in the e-CRF that occur any time after informed consent is obtained until 7 days (for non-serious AEs) or 30 days (for SAEs) after the last day of trial participation.

Every SAE will be followed-up until the event is resolved, resolved with sequelae, or until study closure, whichever occurs first.

When required by national or local regulations, the principal investigator shall also notify the EC of all reportable events according to national regulations within the by regulations required timelines and may also be requested by the EC to provide annual reports.

16.1.3 Information provided by the clinical investigation site

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The principal investigator will provide the following information, at a minimum, for each adverse event (AE) or Adverse Device Effect (ADE):

- Date of the AE or ADE onset.
- Date Principal Investigator (or authorized designee) became aware of AE or ADE
- Description of AE or ADE and circumstances (detailed description of course of event)
- Treatment
- Resolution
- Assessment of:
 1. Seriousness
 2. Severity of the event
 - f. Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
 - g. Moderate: minimal, local or noninvasive intervention indicated; limiting
 - h. Severe: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling
 - i. Life-threatening: urgent intervention indicated, disabling
 - ii. Fatal: death related to AE
 3. Relationship of the event to the investigational device (Not related, possible, probable, or causal [definite] relationship).
 4. Relationship of the event to the index procedure (Not related, possible, probable, or causal [definite] relationship)
 5. If not related to study device or study procedure, causality with
 - a. disease under study
 - b. lack of performance of the investigational device or comparator/worsening of treated condition
 - c. medical history (current/past)
 - d. concomitant or previous medication
 - e. technical issue of the other products used
 - f. other (specify)

In addition, the severity of the event will be assessed using a Clavien-Dindo Classification as discussed in section 14.2.

Table 6 displays a list of the reports that are the Principal Investigator's responsibility to generate. The table also shows to whom the report is to be sent, and with what frequency or time constraints. While some of these reports will be developed by or with the assistance of the Sponsor, the final responsibility for them rests with the PI. The responsibilities may be delegated by the Principal Investigator to the Study Coordinator.

Table 6: Reports Required from Clinical Investigators

Type of Report	Prepared by Investigator for:	Time Constraints of Notification
Patient death	Sponsor	Immediately (but not later than 3 calendar days)

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Type of Report	Prepared by Investigator for:	Time Constraints of Notification
Unanticipated adverse event	Sponsor	Immediately (but not later than 3 calendar days)
Report of patient enrollment	Sponsor	Within 5 working days
Serious adverse event that has a causal relationship with the investigational device, or the investigation procedure or where such causal relationship is reasonably possible	Sponsor	Immediately (but not later than 3 calendar days)
Device deficiency that might have led to a serious adverse event	Sponsor	Immediately (but not later than 3 calendar days)
Patient withdrawal	Sponsor	Within 5 working days
Withdrawal of Ethics Committee approval	Sponsor	Within 5 working days
Deviations from investigational plan	Sponsor	Within 5 working days
Informed consent not obtained	Sponsor	Within 5 working days
Final summary report	Sponsor	Within 3 months

16.1.4 Institutional Review Board/Ethics Committee & Regulatory Authorities

Ethics Committee (EC) and Regulatory Authority approval for the study is required prior to beginning the study. A copy of the approvals must be sent to the Sponsor prior to the site initiation.

Any additional requirement imposed by the EC or regulatory authority shall be followed, as appropriate.

16.2 Sponsor Responsibilities

SafeHeal, and/or their designee, is the Sponsor of the clinical study. The Sponsor's responsibilities in the study include to:

- Provide study device to participating study sites, in quantities sufficient to support study activities.
- Provide all training to investigators and study sites staff.
- Select the Principal Investigator, all associate investigators and study sites, and other consultants, who participate in the study.
- Provide financial support to the study sites per individual contracts with each site.
- Subscribe to an insurance policy covering potential risks associated with the usage of the study device in the scope of this clinical study

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- Establish all regulatory standards per national and local regulations for clinical study sites, and other participants, and perform regular site monitoring to assure compliance with them. The ethics committee will be notified by the Study Sponsor of:
 - all unexpected serious device related adverse events (USADEs) immediately, but no later than 5 business days after the sponsor becomes aware of a new reportable event or new information related to a previously reported event.
 - all other serious device-related adverse events (SADEs) shall be reported within 10 business days after the sponsor becomes aware of a new reportable event or new information related to a previously reported event.
- Perform site monitoring of clinical data at the clinical study sites on a regular basis, retain ownership of all clinical data generated in this study and control the use of the data. SafeHeal will exercise no veto over publication of study results in the medical literature but will be provided with advance copies of manuscripts and abstracts to review for technical accuracy.
- Ensure that the study is conducted per protocol requirements. Any deviation will have to be documented as a protocol deviation on the appropriate CRF and reported per national regulations.

16.3 Monitoring

SafeHeal, as the sponsor of this study, is responsible for ensuring that adequate monitoring at each site is completed to ensure protection of the rights and safety of subject and the quality/integrity of the data collected and submitted. However, SafeHeal has transferred certain clinical investigation-related duties and functions, including monitoring, to:

Clinical Accelerator
19-21 Circular Road
Douglas, Isle of Man, IM1 1AF

The Monitoring visits will be conducted at the start, during and at the closure of the clinical study in accordance with a Monitoring Plan developed for this study. The Monitoring Plan includes the frequency of monitoring visits, source data verification procedures and procedures for monitoring subject compliance for this study. Monitors are appropriately trained and qualified to monitor the adherence to the investigational plan, the signed investigator agreement, compliance to the IRB/EC conditions and guidelines and compliance to applicable regulations. Any non-compliance with these items that is not adequately addressed by the principal investigator and/or his/her research site staff is cause for the Sponsor to put the investigator site/staff on hold or withdraw the investigator/site staff from participation in the study. During a monitoring visit, the monitor may review source documents and informed consents for a representative number of subjects and/or CRFs. Frequency of monitoring visits will be based upon enrollment, study duration, compliance and any suspected inconsistency in data that requires investigation. In between monitoring visits, the monitors will maintain personal contact with the Principal Investigator and staff throughout the study by phone and/or e-mail on a regular basis.

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16.4 ISO 14155 Compliance

This clinical study will be conducted in accordance with the standard EN ISO 14155:2020 and the recommendations guiding physicians in biomedical research involving human subjects adopted by the World Medical Assembly, Helsinki, Finland, 2013 and later revisions.

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17.0 Revision History

Ver.	Change	Date
0	Original Issue	15 Aug 2023
1	<ul style="list-style-type: none"> Modified Inclusion criterion 2 to restrict population to subjects with planned diverting loop ileostomy for malignancy, based on multidisciplinary team recommendations. Modified Exclusion criterion 5a to better define metastatic disease Added Exclusion criterion 6 f) to restrict population to subjects with an anastomosis within 15 cm of anal verge. Updated Colovac 2 and SmartVac device descriptions Added Staff Ease of Device Use, Subject Tolerance and Ease of Use of Device, and Retrieval Usability Questionnaires Increased frequency of CRP and WBC collection from every 2 days to daily during hospitalization 	12 Apr 2024
2	<ul style="list-style-type: none"> Added endoscopic evaluation of the mucosa at the 1-month visit Updated investigational device management to include CRO and align with Device Management Plan Added ISREC grading of anastomotic leaks Updated safety assessment and reporting to align with Safety Management Plan 	12 Sep 2024

18.0 References

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19.0 Abbreviations

Abbreviation/Term	Definition
AE	Adverse Event
AL	Anastomotic leakage
BBPS	Boston Bowel Preparation Scale
CRP	C-Reactive Protein
CT	Computed Tomography
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EU	European
FDA	Food and Drug Administration
GDPR	General Data Protection Regulation
ICF	Informed Consent Form
IDE	Investigational device exemption
IFU	Device Instructions for Use
IRB	Institutional review board
ISREC	International Study Group of Rectal Cancer
OUS	Outside of the United States
PI	Principal Investigator
QOL	Quality of life
SADE	Serious Adverse Device Events
SAE	Serious Adverse Event
TME	Total Mesorectal Excision
UADE	Unanticipated adverse device effect
USADE	Unanticipated Serious Device Adverse Effect
US	United States
WBC	White Blood Cell

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20.0 Appendices

- Appendix 1: ECOG Performance Status Score
- Appendix 2: Boston Bowel Preparation Scale score
- Appendix 3: ISREC grading

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20.1 Appendix 1: ECOG Performance Status Score

ECOG Performance Status Scale

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982 Dec;5(6):649-655. PMID: 7165009.

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20.1 Appendix 2: Boston Bowel Preparation Scale (BBPS)

Diversion of the fecal stream will be assessed using the BBPS score below:

BBPS Score	Description
0	Unprepared colon segment with mucosa not seen due to solid stool that cannot be cleared.
1	Portion of mucosa of the colon segment seen, but other areas of the colon segment not well seen due to staining, residual stool and/or opaque liquid.
2	Minor amount of residual staining, small fragments of stool and/or opaque liquid, but mucosa of colon segment seen well.
3	Entire mucosa of colon segment seen well with no residual staining, small fragments of stool or opaque liquid.

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20.2 Appendix 3: ISREC Grade

Anastomotic leaks will be graded according to the ISREC grading system that classifies ALs into one of three grades based on severity and required treatment. The ISREC grades are defined as follows:

- Grade A anastomotic leakage is identified by radiographic findings of a perianastomotic fluid collection, leakage of contrast through the anastomosis, or observation of new drainage of enteric contents through either a drain or through a fistula but without accompanying clinical complaints. These may be managed expectantly. These may become apparent during the preoperative work-up prior to closure of a diverting ostomy and will at least delay reversal.
- Grade B anastomotic leakage requires therapeutic intervention but does not necessarily require reoperation. Antibiotics and percutaneous drainage of fluid collections are the most common nonoperative interventions.
- Grade C anastomotic leakage requires repeat laparotomy. Surgical treatment is performed with the goal of controlling life-threatening sepsis. The traditional operation with takedown of the anastomosis and end colostomy may be appropriate, but washout with drain placement and diverting loop ileostomy may also be appropriate.