SafeHeal
Reshaping Colorectal Surgery

SafeHeal Colovac Colorectal Anastomosis Protection Device Evaluation (SAFE-2) Pivotal Study

A Study to Evaluate the Safety and Effectiveness of the Colovac Colorectal Anastomosis Protection Device

Clinical Study Protocol/

Clinical Investigation Plan

Version 2.0

August 30, 2022

US Sponsor: **SafeHeal Inc**.
800 Village Walk, Suite 126
Guilford, CT 06443

EU Sponsor: **SafeHeal SAS**
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75002 Paris, France

Version History

Version and Date	Summary of Major Changes	Author(s)/Title
1.1 30Apr2019	• Not Applicable, New Document	Claire Chappert, Director of Clinical & Regulatory Affairs
1.2 26May2020	• Removed Genae as CRO • Increased sample size • Primary and secondary endpoints changed • Defined clinically significant migration • Modified inclusion/exclusion criteria • Aligned potential adverse events with IFU • Added treatment algorithm flowchart • Updated statistical analyses	Claire Chappert, Director of Clinical & Regulatory Affairs
1.3 24Oct2020	• Added run-in component with Usability eCRF • Change mucosal grading and added CEC review of mucosa using endoscopic video • Added sigmoidoscopic anastomosis evaluation at 6 and 12-months • Detailed the location of the anastomosis (10 cms from anal verge) • Removed legally authorized representative option for consent • Added Hart Clinical Consultants as CRO • Added MiniEnema as recommended lubricant • Added JetVAC bottles as vacuum bottles that could be supplied	Claire Chappert, Director of Clinical & Regulatory Affairs
1.4 09Apr2021	• Changed run-in component to non-randomized subjects • Increased sample size by 20 non-randomized Colovac subjects for run-in component • Added endoscopic evaluation of fecal diversion as a secondary endpoint • Modified primary effectiveness endpoint • Added subgroup analyses • Added the BBPS for endoscopic assessment of fecal diversion • Added the ISREC AL grading system • Added Complete Case sensitivity analysis • Added covariates for multiple imputation • Added analysis of poolability of data • Updated the treatment algorithm flowchart • Added AL relatedness flowcharts for Colovac and Control groups	Claire Chappert, Director of Clinical & Regulatory Affairs
1.5 26May2021	• Added instruction on application of lubricant to the tip of the stent • Added use of SafeHeal Vacuum Loss Alert System and Hollister Horizontal Drain/Tube Attachment, • Added required baseline x-ray documenting device position and additional optional x-rays documenting device position	Claire Chappert, Director of Clinical & Regulatory Affairs

	• Modified informed consent procedures • Modified Appendices Listing • Minor modifications for clarity/consistency and to correct typographical error • Clarified publication policy and added CMS coverage information	
1.6 5Aug2021	• Changed recommendation against laxatives to antidiarrheal medication such as Loperamide (Imodium) • Clarified the vacuum tube attachment instructions • Clarified that device monitoring is performed twice daily • Updated adverse event reporting to comply with ISO14155:2020 • Modified Appendices Listing • Minor modifications for clarity/consistency and to correct typographical errors	Claire Chappert, Director of Clinical & Regulatory Affairs
1.7 03Mar2022	• Increased the number of US sites to a maximum of 15 and the run in arm to a maximum of 30.Modified intended use from “reduction of contact of fecal content” to “limit stoma creation to only those patients requiring more time for anastomosis healing” and “intended for use in patients requiring low anterior rectal anastomoses” • Modified primary effectiveness study objective from “…in diverting the fecal stream from anastomosis site …” to “…in reducing the stoma creation rate” for Colovac subjects • Defined primary effectiveness success • Changed the primary effectiveness endpoint to a clinically meaningful reduction in stoma creation rate in Colovac subjects at 12 months and added the performance goal for this endpoint • Changed the composite endpoint to a secondary effectiveness endpoint and added its components as secondary effectiveness endpoints. • Removed ostomy conversion rate from secondary endpoint as it is primary endpoint • Removed the proposed performance goal for the secondary composite endpoint and the appendix with the Performance Goal Meta-Analysis Publication • Changed the Objectives to be consistent with changes to the effectiveness endpoints • Changed the Colovac Implantation Procedure for consistency with the IFU • Refined definition of a clinically significant anastomotic leak to include a combination of ISREC and Clavien-Dindo	Dawn Tolbert, Director Clinical Affairs

	• Changed the Day 9 interval to +3 days • Added endoscopic assessment of the anchoring site at 6 and 12 month post-surgery • Added subgroup analysis re: surgical approach and anastomosis location • Corrected post-surgery typo re: secondary objective • Made trimming of sheath optional • Modification of CT requirement from triple to double contrast (eliminated oral) • Added recommendation for monitoring of stool consistency • Added a general complication of any colorectal surgery for consistency with the IFU • Added urgent CEC review of events in the study stopping criteria; added list of study stopping criteria and DSMB ad hoc meeting triggers. Removed requirement of assessment of protocol deviations by CEC • Added ad hoc meeting if any of the study stopping criteria trigger DSMB review of the events • Updated summary of DSMB charter • Modified Suspension or Premature Termination Section for consistency with DSMB Section and DSMB Charter • Added relationship to VLAS as part of the AE assessment • Removed specified lubricant and referred to the IFU for recommendations • Added instructions to obtain a still image and a video during post-retrieval endoscopic examination. • Removed investigator assessment of anticipatedness of AEs • Updated Investigator reporting requirements to align with European MDR. • Added EU Sponsor • Added the NCT registration number of the trial • Recalculated sample size for updated primary effectiveness endpoint using an adaptive design • Added a per site enrollment cap of 20% • Harmonized Adverse Event Definitions with ISO 14155:2020 and 21 CFR812 • Added use of the MDCG 2020-10 template to report the SAEs to the NCAs of EU member states • Added procedure for protocol amendments per EU requirements • Added procedure for the end of the investigation per EU requirements • Added clarifications	

	• Corrected typographical errors	
2.0 30Aug2022	• Updated Potential Adverse Effects List • Added request for video recording of the run in Colovac implantations	Claire Chappert, VP Clinical Affairs

INVESTIGATOR SIGNATURE PAGE

I have read and understand the attached protocol entitled "A Study to Evaluate the Safety and Effectiveness of the Colovac Colorectal Anastomosis Protection Device" and agree to abide by all described protocol procedures. I agree that this study will be conducted according to all stipulations of the protocol and attachments, including all statements regarding confidentiality, and according to local and applicable federal regulations.

Site Principal Investigator:

Signature
Printed Name
Date

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Note that Appendices are kept separately; thus, updates to any of these appendices will not require the protocol to be updated.

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SYNOPSIS

Scope	This is a pivotal, multicenter, prospective, randomized, open-label controlled trial clinical trial that aims to evaluate the safety and effectiveness of the Colovac Colorectal Anastomosis Protection Device compared to the standard of care (diverting ostomy). Subjects are randomized 1:1 to standard of care treatment (control group) or Colovac device treatment (treatment group). Additionally, to assess any deployment challenges or technical difficulties, and capture any adverse events that occur during Colovac implantation, the study includes a run-in component that will include the first two Colovac subjects for the PI at each US site. For the randomized component, this pivotal study aims to enroll a total of 342 patients (171 patients in the control group and 171 in the treatment group) at up to 15 sites in the US and up to 10 sites in the EU. For the non-randomized run-in component of the study, a maximum of 30 subjects (2 subjects at each US site) will be enrolled. Additionally, European sites with no experience implanting the Colovac device will enroll 2 subjects per site in a European run-in component. However, the IDE sample size will not be increased for these OUS subjects as they will not be included in the randomized cohort.
Investigational Device	Colovac Colorectal Anastomosis Protection Device
Device manufacturer	Contract Medical International GmbH (CMI), Germany Lauensteiner Strasse 37 01277 Dresden, Germany +49 351 213 8888 Office
Expected study duration	Enrollment: 8-12 months FU period: 12 months Total expected study duration: 20-24 months
Follow-up Visits	Daily while hospitalized, 9 Days, 1 Month, 3 Months, 6 Months, 9 Months and 12 Months
Sponsor	**US:** **SafeHeal Inc.** 800 Village Walk, Suite 126 Guilford, CT 06443 **EU:** **SafeHeal SAS** 9 rue du 4 Septembre, 75002 Paris, France

Primary Objectives	The primary study objectives are: 1) To assess the safety of the Colovac device by comparing the rate of major complications, as defined in the protocol; and To assess the effectiveness of the Colovac device in reducing the stoma creation rate.
Primary Endpoints	The primary safety endpoint is the rate of subjects with post-operative major complications within 12 months. The primary effectiveness endpoint assessed for all subjects in the Colovac arm at 12 months is a clinically meaningful reduction in stoma creation rate.
Secondary Objectives	The secondary objectives of the investigation are: To compare the cumulative length of hospital stay within 12 months post-discharge To provide an additional assessment of product safety via the Comprehensive Classification Index (CCI) To evaluate patient quality of life via the LARS Score within 12 Months To evaluate patient quality of life via the EQ-5D-5L Quality of Life within 12 Months To assess the performance of the Colovac device in diversion of fecal stream, avoidance of clinically significant and symptomatic AL, and avoidance of clinically significant migration To evaluate diversion of fecal stream assessed by endoscopic evaluation before device removal To evaluate the absence of clinically significant and symptomatic leak. To evaluate avoidance of clinically significant migration To evaluate the mucosal appearance (integrity of the anchoring site) and the integrity of the anastomosis after the device retrieval To evaluate the integrity of the anchoring site at 6 and 12 months To assess the patient acceptance and tolerability of the device, during the Colovac Device implantation period
Secondary Effectiveness Endpoints	The secondary endpoints are: <u>For Comparison between the Colovac and Control Arms:</u> Cumulative length of hospital stay during the 12 months post-discharge Comprehensive Classification Index (CCI) Patient Quality of Life: LARS Patient Quality of Life: EQ-5D-5L

	Assessment of anastomosis at 6 and 12-months post-surgery <u>For Colovac Only:</u> The following composite endpoint will be assessed at Day 10: Diversion of fecal stream from the anastomosis site confirmed by endoscopic evaluation for the absence of feces between the sheath and the colonic wall AND the absence of clinically significant and symptomatic leak; AND Absence of clinically significant migration Diversion of fecal stream from the anastomosis site confirmed by endoscopic evaluation for the absence of feces between the sheath and the colonic wall Absence of clinically significant and symptomatic leak Absence of clinically significant migration Elective ostomy conversion within 12 months after index surgery Assessment of mucosal appearance after device retrieval Assessment of anastomosis integrity after device retrieval Patient acceptance and tolerability of the Colovac Device Assessment of anchoring site at 6 and 12 months post-surgery
Inclusion Criteria	Candidates for this study must meet ALL of the following criteria: Adult patients (18 years of age or older) Eligible to undergo open or minimally invasive sphincter-sparing low anterior resection (anastomosis within 10 cm of the anal verge) with planned diverting loop ileostomy for malignancy, based on multidisciplinary team recommendations. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2 Willing 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: <u>Preoperative</u> History of left colitis Known allergy to nickel or other components of the Colovac kit Pregnant or nursing female subject Concomitant major surgical procedure in combination with Colorectal resection (e.g., hepatectomy) 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: COVID-19 positive (active infection) based on test within 48 hours prior to surgery Immunodeficiency (CD4+ count < 500 mm^3) Systemic steroid therapy within the past 6 months Systemic infection at the time of surgery or requiring systemic antimicrobial therapy up to 1 week before surgery Major surgical or interventional procedures within 30 days prior to this study or any planned surgical or interventional procedures within 30 days of entry into this study Diagnosis of bowel obstruction, bowel strangulation, peritonitis, bowel perforation, intraabdominal infection, ischemic bowel, carcinomatosis Fecal incontinence, involvement of sphincter by the neoplastic disease or evidence of extensive local disease in the pelvis seen on pre-operative imaging Severe Malnutrition defined as ≥ 10% weight loss within 3 months prior to enrollment.

	The subject is currently participating in another investigational drug or device study Intraoperative Occurrence of any of the following during the colorectal surgery: Blood loss (>750 cc) Blood transfusion Any new sign of ischemia Positive air leak test – requiring re-intervention on the anastomosis Inadequate bowel preparation Anastomosis location greater than 10 cm from the anal verge Other intra-operative risks that preclude the subject from undergoing the procedure with the investigational device

Schedule of Events

Schedule of Pre-Randomization Procedures		
Procedure	**Pre-Operative Day -1 (-44 days)**	**Intraoperative (Index Surgery) Day 0**
Informed Consent Signed	X	
Medical Billing Release Form*	X	
Screening/Preliminary Eligibility Determination	X	
Medical History and Physical Examination	X	
EQ5D QOL	X	
LARS QOL	X	
Low Anterior Resection Procedure (Index Surgery)		X
Surgery eCRF		X
Final (Intraoperative) Eligibility Determination		X
Screen Failure or Randomization		X

*Optional collection of financial information related to costs of medical treatment for future use outside this IDE in a health economics study.

Schedule of Study Procedures: Control Arm									
			Follow-up						
Procedure	**Surgery Day 0**	**Hospital Day 1- 5* Daily**	**Day 9 (+3 days)**	**1 Month (±14 days)**	**3 Months (±14 days)**	**6 Months (±30 days)**	**9 Months (±30 days)**	**12 Months (±45 days)**	**If/when applicable**
Ostomy Creation	X								
Daily Clinical Eval		X							
CRP		X**							
WBC, Hemoglobin			X	X	X	X	X	X	X
Contrast CT Scan of Anastomosis			X						
Anastomotic Test eCRF			X						
EQ5D QOL			X	X	X	X	X	X	
LARS QOL***				X	X	X	X	X	
Sigmoidoscopic Evaluation of Anastomosis						X		X	
AEs	X	X	X	X	X	X	X	X	X****
Ostomy Reversal									X

*The actual length of hospitalization will vary based on individual patient factors. Daily follow-up will be performed as long as the subject is hospitalized.
**Starting on Day 2, CRP will be tested every 2 days during hospitalization
***LARS QOL will only be collected at follow-up visits after ostomy reversal
****AEs related to the stoma reversal procedure will be collected

Schedule of Study Procedures: Colovac Arm										
		Hospitalization			Follow-up					
Procedure	Surgery Day 0	Day 1-8 Daily	Day 9 (+3 days)	Day 10 (-1/+2 days)	1 Month (±14 days)	3 Months (±14 days)	6 Months (±30 days)	9 Months (±30 days)	12 Months (±45 days)	If/when applicable
Colovac Insertion	X									
Usability Questionnaire	X*									
Device Position X-ray	X**	X**	X**							
Daily Clinical Evaluation		X	X							
CRP		X***								
WBC, Hemoglobin					X	X	X	X	X	
Daily Study Evaluation		X	X							
Trim Sheath		Day 2 only								
Contrast CT Scan of Anastomosis			X							
Endoscopic Evaluation of Colon (BBPS score)				X†						
EQ5D QOL			X		X	X	X	X	X	
LARS QOL‡			X		X	X	X	X	X	
Colovac Retrieval				X						
Conversion to Ostomy										X
Endoscopic Examination of Mucosa Post-retrieval				X						
Evaluation of Anastomosis Post-retrieval				X						
Retrieval eCRF				X						
Sigmoidoscopic Evaluation of Anastomosis and Anchoring Site							X		X	
AEs	X	X	X	X	X	X	X	X	X	X§
Ostomy Reversal										X

*The Usability Questionnaire will be completed for first two Colovac subjects for the PI at each US to assess any deployment challenges or technical difficulties that occur during Colovac implantation.

**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.

***Starting on Day 2, CRP will be tested every 2 days during hospitalization

†If device is removed before Day 10 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

‡If subject is converted to diverting ostomy, LARS QOL will only be collected at follow-up visits after ostomy reversal.

§AEs related to the stoma creation or reversal procedure will be collected

ABBREVIATION/TERM WITH DEFINITION

Abbreviation/Term	Definition
AE	Adverse Event
AL	Anastomotic leakage
BBPS	Boston Bowel Preparation Scale
CCI	Comprehensive Classification Index
CEC	Clinical Evaluation Committee
CMI	Contract Medical International
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EU	European
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
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
LARS	Low Anterior Resection Syndrome
ml	Milliliter
MPI	Mannheim Peritonitis Index
NB	Notified Bodies
NCA	National Competent Authorities
OUS	Outside of the United States
PG	Performance Goal
PI	Principal Investigator
QOL	Quality of life

Abbreviation/Term	Definition
SADE	Serious Adverse Device Events
SAE	Serious Adverse Event
SSI	Surgical Site Infection
TME	Total Mesorectal Excision
UADE	Unanticipated adverse device effect
USADE	Unanticipated Serious Device Adverse Effect
US	United States
VAS	Visual Analogue Scale
VLAS	Vacuum Loss Alert System

INTRODUCTION AND BACKGROUND

COLORECTAL SURGERY

Colorectal cancer is the third most common malignancy worldwide and the second most common in the US[1]. It is the second leading cause of cancer death worldwide, with 1.8 million new cases and 862,000 deaths per year[2]. The majority of patients receive surgical treatment[3]. 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%[4]. Postoperative complications occur in up to 43% of patients undergoing colorectal procedures[5]. Major postoperative complications include surgical site infection, ileus, bleeding and anastomotic complications.

The most serious 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.

Known risks for anastomotic leakage include distance of anastomosis location from the anal verge and decreased perfusion of the proximal colon/conduit[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[21]. Many of these are major complications that are more severe, requiring comprehensive interventions and therapies that include hospitalization and surgical procedures. The major complications related to anastomosis are anastomotic leakage[7,8,9,14,10,11,12,13], anastomotic stricture[11,12,] anastomotic bleeding[7], abscess[7,8,9,14,15], bowel

obstruction[16,9,17,18], sepsis and shock[9,19], and ileus[8,19,14]. Some major complications require blood transfusions[14] and some result in death[7,16,20,8,9,19]. Additional major complications reported include wound complications, internal hernia, obstructive uropathy, urethral stricture and rectovaginal fistula[7,12,15].

Protection of the anastomosis with an ostomy may limit the incidence of clinically manifest anastomotic leakage by as much as 30%[21]. Thus, the large majority of patients undergoing low anterior resection of the rectum with Total Mesorectal Excision (TME), the standard of care for rectal cancer, typically undergo creation of a temporary ostomy due to the relatively high risk of anastomotic leakage.

STANDARD OF CARE OSTOMY

To minimize the consequences of an anastomotic leakage following high-risk colorectal low anterior resections, a temporary ileostomy (also known as a loop or diverting ostomy) is usually created to prevent leakage of fecal content into the abdominal cavity in case of anastomotic complications. Although the anastomosis typically heals in less than 10 days, ostomy reversal is usually deferred up to 6 months post resection based on the need for adjuvant therapy.

However, ileostomies are associated with a significant risk of postoperative complications which can be as high as 43%[5], including dermatologic complications (peristomal skin breakdown), parastomal hernia, stoma necrosis, prolapse or retraction, obstruction and dehydration from high-output of the stoma. Although many of these complications are mild in severity and resolve with simple treatment, others are more severe, major complications, requiring treatment that includes hospitalization and surgical procedures. The major complications related to ileostomy include dehydration from high-output stoma[11,18] , ileus[27,10,22] , stomal prolapse[27,23], wound complications[27], and parastomal hernia [23], Other more severe complications reported include necrosis, stenosis, and peritonitis[23],[15].

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 [9,19,15,24]. 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[25].

ALTERNATIVE TO OSTOMY

In light of all 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 cover the anastomosis temporarily and reduce the clinical impact of a potential fistula.

The SafeHeal Colovac 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.

It postpones the decision to perform diverting stoma until anastomotic healing can be assessed, and selectively reserves the use of diverting stoma for only those patients with evidence of incomplete anastomotic healing.

INVESTIGATIONAL DEVICE PRELIMINARY CLINICAL DATA

The following data were collected in a feasibility study, SAFE-1 (NCT03352570). This multicenter, open label study of the Colovac device enrolled 15 patients between November 2017 and June 2018. The objective of the SAFE-1 study was to provide an initial assessment of performance and safety of the device compared to published results of the standard of care, LAR with diverting ostomy. The procedural and 14-day safety results of the Colovac device were the key determinants of clinical success in the study.

SAFETY

The occurrence of serious adverse events during the Colovac implantation period was compared to the complication profile of the standard of care procedure, LAR with diverting ostomy.

Intraoperative Period

No intra-operative serious adverse events were reported. Transanal introductions of the device did not present any complications for the subjects or the anastomotic sites. One device was accidently pulled distally during withdrawal of the introducer. This device was immediately removed and quickly replaced with another one with no complications or additional difficulty.

Implantation Period

During the implantation period, 3 subjects experienced device migration and anastomotic leakage (AL). One case of migration was secondary to device misplacement, and two were secondary to a loss of vacuum between the stent and the colon wall due to a technical malfunction of the vacuum tube. All cases of migration were managed by ostomy creation as a safety measure per protocol.

The following measures were taken to prevent/reduce the occurrence of the above-mentioned device migration in the proposed SAFE-2 Pivotal Study:

- Implemented technical design changes to the device to improve vacuum control
- Improved Instructions for Use:

  Regarding the placement of the device, it is now recommended to place the proximal (downstream) edge of the stent component of the Colovac device above the top of the sacral promontory. This eliminates the need to measure the distance from the anastomosis site and allows visual confirmation of correct device placement.

In addition, the following procedures have been added to the SAFE- 2 Pivotal Study procedures:

Perform daily checks of both connections at the level of the anus and at the vacuum source.

Monitor daily the amount of fluid collected in the vacuum system bottle (Always suspect a loss of vacuum if no fluid is collected).

Measure daily the length of the external sheath to identify early signs of migration

In cases of suspected device migration below the sacral promontory, obtain a CT scan of the abdomen and pelvis to evaluate current stent location compared to the Sacral Promontory (using standard anatomical landmarks).

Good tolerance of the device was demonstrated by subjects, with no reports of major discomfort and only reports of limited discomfort related to the vacuum channel and external sheath.

Device removal

Transanal retrievals of the device did not present any complications for the subjects or the anastomotic sites. In all cases, the Colovac device was easily extracted and the anastomosis showed no evidence of injury. Following device removal, the mucosal appearance above the anchoring site and at the anastomotic site was rated as normal or inflammatory in 80% of cases and as bleeding or ulcerated in 20%. None of the subjects required treatment or further surveillance. At the device anchoring site, small bleeding lesions that required no treatment or further surveillance were reported in 27% of patients. In all these cases, the anastomosis was healed and successful diversion of fecal matter by the Colovac device was confirmed.

Post-implant period (3 Months)

The most commonly reported adverse event recorded in the 3 month follow-up period was late pelvic collections (20%). The occurrence of a pelvic collection more than 8 days after the Colovac retrieval may signal potential for a late fistulation, as reported in the literature. After early ostomy closure (between 7 and 14 days), the study from Alves and al[26] reports a leakage rate of 1 - 4 %, which is supported by the Yin and al. study (Yin et al. 2017)[27]. After early ostomy closure (between 14 and 28 days), Nelson and al. reported intra-abdominal collection rate at 14% (Nelson et al. 2018)[28]. These observed complication rates (abscess / leak) with early closure of fecal diversion are similar to what has been observed with Colovac alternative anastomosis protection. All pelvic complications were successfully treated without hospitalization and their anastomoses healed.

Other reported adverse events included: seizures in one patient (7%) and bowel obstruction in one patient (7%). These adverse events were not related to the device based on review by the SAFE-1 Study Data Safety Monitoring Board.

EFFICACY

The Colovac device provided effective diversion of feces in all 12/15 (80%) subjects where the device remained implanted during the entire 14-day implantation period. In all 12 cases, the anastomosis was protected. Additionally, the Colovac device allowed avoidance of stoma creation in 10/15 (67%), who otherwise would have undergone stoma creation as the standard of care.

Avoidance of a stoma is expected to significantly reduce the morbidity and cost associated with stoma creation and closure, as well as improve the quality of life of patients undergoing LAR for rectal cancer. The Colovac objective is to reduce the number of diverting ostomies by providing temporary, minimally-invasive protection of the anastomosis. Regardless of the efficacy of the Colovac at protecting the anastomosis, it is anticipated that a proportion of subjects will still demonstrate incomplete anastomotic healing at the time of device removal and will require a diverting stoma to provide longer-term anastomotic protection. Incomplete anastomotic healing results from unforeseen local factors, such as ischemia or mechanical tension[29].

Results obtained in the SAFE-1 study of 15-subjects implanted with the Colovac device support these assumptions. The incidence of asymptomatic AL (incomplete healing at time of device removal) in the study 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 %)[5,21].

Subjects whose anastomosis was not completely healed underwent delayed stoma creation to provide longer-term protection of their anastomosis. There were no major complications related to stoma creation. All fecal diversion surgeries were planned, and none of the subjects required emergency surgery for symptomatic AL.

Also, we observed a trend towards delayed anastomotic healing and higher risk of anastomotic fistula among subjects with more advanced tumor stages and/or when colorectal resection was combined with an additional surgical procedure (for instance hepatectomy). This data suggests that a 14-day protection period may be too short for this high-risk group of patients. Thus, further adjustments in the study protocol now include more stringent patient selection to exclude these higher-risk patients.

Conclusions Regarding the Safety and Effectiveness

Results of 15 subjects enrolled in the feasibility study include;

Effective diversion of feces was confirmed in all 12/15 (80%) subjects where the device remained implanted during the entire 14-day implantation period. Thus, the Colovac device provided effective protection of the anastomosis in all 12 subjects.

The Colovac device allowed avoidance of stoma creation in 10/15 (67%) subjects with complete anastomotic healing at the time of device removal. These subjects would otherwise have undergone stoma creation as the standard of care. The 2 cases of incomplete anastomotic healing underwent non-emergent stoma creation without any major intra-operative complications.

Device migration was reported in 3/15 (20%) subjects due to device malfunction (2 subjects) and misplacement of the device (1 subject) and required a non-emergent conversion to standard of care diverting ostomy

In the 3-month follow-up period, late pelvic collections were reported in 20% of the subjects. This rate is similar to the 14% rate of intra-abdominal collection rate after early ostomy closure (between 14 and 28 days) and the 18% rate after conventional closure reported by Nelson and al.[28]. All subjects were

treated with antibiotics. Additionally, one had anastomotic clips placed endoscopically and one had a drain inserted. All the pelvic collections resolved, and the subjects had no further complications.

One device was accidently pulled distally during withdrawal of the introducer. This device was immediately removed and quickly replaced with another Colovac device with no complications or difficulty.

Transanal retrievals of the device did not present any complications for the subjects or the anastomotic sites. In all cases, the Colovac device was easily extracted and the anastomosis showed no evidence of injury. Based on mucosal appearance above the anchoring site and at the anastomotic site following device removal, no treatment or further surveillance was required.

Furthermore, with technical design changes to the device, further improvement in device placement instructions, refined patient selection criteria and additional study procedures to more closely monitor device migration, the proportion of patients who may avoid stoma creation with Colovac implantation is expected to increase and the incidence of device migration is expected to decrease.

OVERALL SAFE-1 STUDY CONCLUSION

This initial study provided the first evidence that this novel concept was well-tolerated by patients. Limited discomfort related to the presence of a drain and a sheath through the anus were reported during the implant period, which must be viewed in the context of the discomfort associated with the ostomy for a much longer period of time. For the purpose of the study, patients were not discharged before the end of the implantation period, but earlier patient discharge could be envisioned in the future.

The results of the study show that Colovac provides a local, temporary, non-invasive protection of the anastomosis during its healing process, avoiding the need for a diverting ostomy for patients who do not experience anastomotic complications or incomplete healing, and allowing safe conversion to standard of care diverting ostomy for patients requiring prolonged anastomotic protection. The data from the study were instrumental in identifying changes to the product design, patient selection criteria and instructions for use, including adding procedures to more closely monitor for device migration, that would result in Colovac becoming an even more effective patient management alternative for patients undergoing low anterior resection.

STUDY RATIONALE

A feasibility study (SAFE-1, NCT03352570) of the first design of the Colovac device enrolled 15 patients between November 2017 and June 2018. The objective of the SAFE-1 study was to provide an initial efficacy and safety assessment. Promising safety and performance results have emerged from this investigation. This device obtained CE mark on 7 March 2019.

Based on these first results and investigator feedback, a second version of the device has been developed. Incremental changes have been made to meet all biocompatibility requirements, mitigate the risk of migration, and facilitate the daily monitoring of the device during the implantation period. These changes include modifying the stent to an overlapping configuration of two stents to create additional passages for air evacuation when the vacuum is applied; adding a redundant vacuum tube and drain; adding markings on the sheath and vacuum tubes for ease in detecting possible device migration; adding stent passivation and electropolishing to improve corrosion resistance and biocompatibility; and pre-cutting one “petal” of the molded tulip tip to improve deployment of the stent during insertion.

Following the feasibility study, this pivotal study aims to collect clinical data on a larger treatment group to confirm the safety and effectiveness of the Colovac Anastomosis protection device. The Colovac Device implantation period has been changed from 14 days in the SAFE-1 Study to 10 days in this study based on the results of animal study. As reported by Oxlund et al.[30], the mechanical strength of a wound that is healing depends on the deposition of collagen fibrils across the wound cleft. The fibrils degrade and remodel which further increases the mechanical strength of the wound. In a study of colon anastomoses in rats, Oxlund et al. showed that collagen deposition in the colon reached a maximum at post-operative day 6 with a corresponding increase in the mechanical strength of the colon wound.

RISK AND BENEFIT RATIONALE

POTENTIAL BENEFIT

The potential benefit for the patient as compared to standard of care ostomy are to:

- Provide a 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.

- Potentially avoid the creation of a stoma (and avoid stoma-related complications) by postponing the decision to perform diverting stoma until anastomotic healing can be assessed, and selectively reserve use of diverting stoma for only those patients with evidence of incomplete anastomotic healing,

- Potentially avoid the need for stoma reversal 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)

ANTICIPATED RISK

Risks to the patient are minimized due to:
The use of standard medical grade materials that have been thoroughly tested to assure biocompatibility
Extensive pre-clinical evaluation including in vitro bench and ex vivo testing, and animal studies
The clinical usage of equivalent devices with minimal safety concern
The well-established, standard nature of the surgical procedures and techniques to be used
The ability to quickly and safely remove the Colovac Anastomosis Protection Device from the patient during or after procedure; the physician may elect to discontinue the use of the device at any time in favor of alternate devices or to convert the anastomosis protection to a diverting ostomy.

The Colovac Colorectal Anastomosis Protection Device related risks have been assessed according to the ISO 14971 with the failure mode and effects analysis method. Residual risks associated with the investigational device, typical for the intended use and type of product, are intended to be mitigated and controlled by specific training of the investigators.

Residual risks are listed below:

Stent migration. Physician may decide to convert the patient to standard of care ostomy if the protection of the anastomosis is compromised.
Need for a conversion to standard of care ostomy in case of incomplete anastomosis healing at the end of the Colovac Anastomosis Protection Device implantation.

According to SAFE-1 Study results, all stoma creations were planned, and not performed in emergency due to clinical symptoms of the patients.

Mucosal injury at the anchoring site

In the SAFE-1 Study, the mucosal appearance was endoscopically evaluated and rated as normal or inflammatory in 80% of cases and as bleeding or ulcerated in 20%. None of the subjects required treatment or further surveillance. At the device anchoring site, small bleeding lesions that required no treatment or further surveillance were reported in 27% of patients.

General complications of colorectal stents, as described in our Instructions for Use.

RISK TO BENEFIT RATIONALE

The SafeHeal Colovac Colorectal Anastomosis Protection Device is used to reduce contact of fecal content with the anastomotic site, following open, laparoscopic, or robotic-assisted laparoscopic colorectal surgery.

It postpones the decision to perform diverting stoma for up to 10 days (after anastomotic healing can be assessed), and selectively reserves the use of diverting stoma for only those patients with evidence of incomplete anastomotic healing.

Patients treated within the stoma pathway will undergo two surgeries under general anesthesia: the index surgery and the stoma reversal surgery.

Depending on their anastomotic healing process, patients treated within the Colovac pathway will undergo either a single surgery – the index surgery, or three surgeries under general anesthesia: the index surgery, the stoma creation surgery after the end of the Colovac implantation period and the stoma reversal surgery.

During the SAFE-1 human trial, the Colovac Colorectal Anastomosis Protection Device demonstrated the potential to eliminate the need for a diverting stoma and associated stoma creation and stoma reversal complications in 67% of patients undergoing LAR for low rectal cancer without any major complications during the three month follow up period. The remaining 33% of patients were converted to standard of care.

Considering the avoidance of stoma related complications and the absence of complications after Colovac retrieval, the benefit of the treatment appears to exceed the risks of implantation of the Colovac Colorectal Anastomosis Protection Device for the majority of patients who won’t experience anastomotic leak.

For the minority of patients who demonstrate an anastomotic leak and will be converted to standard of care, the risk associated with the conversion to stoma at the end of the Colovac implantation period,

meaning the risk of undergoing a second surgery only ten days after the index surgery, is considered as acceptable.

INVESTIGATIONAL DEVICE

The Colovac Colorectal Anastomosis Protection Device Instructions for Use (IFU) is available in Appendix 1.

DEVICE IDENTIFICATION

Device name: Colovac Colorectal Anastomosis Protection Device (Colovac Kit)

Device reference: FG-02788

LEGAL MANUFACTURER

The product is legally manufactured by:

Contract Medical International GmbH (CMI)
Lauensteiner Strasse 37
D-01277 Dresden, Germany

INTENDED USE

The SafeHeal Colovac 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.

The SafeHeal Colovac Device is indicated for use following open, laparoscopic, or robotic-assisted laparoscopic colorectal surgery in patients indicated for diverting ostomy.

DEVICE DESCRIPTION

DEVICE DESCRIPTION

The Colovac Device (Figure 2) is a temporary intraluminal fecal management device, which reduces contact of fecal content with the colorectal anastomotic site, following colorectal surgery.

The Colovac Device is a sterile, single use, disposable device. The kit consists of an Introducer pre-loaded with the Colovac Device.

Note: The Colovac Device is designed to be used in conjunction with:

A standard CE marked or FDA cleared high-vacuum drainage system, using 600ml (ASEPT or JetVAC brands at US sites and ASEPT or Redon brands at OUS sites); and
The SafeHeal Vacuum Connector.

Additionally, the Colovac Device may be used with the SafeHeal Vacuum Loss Alert System.

The device is pre-loaded into the tip of an Introducer (Figure 1).

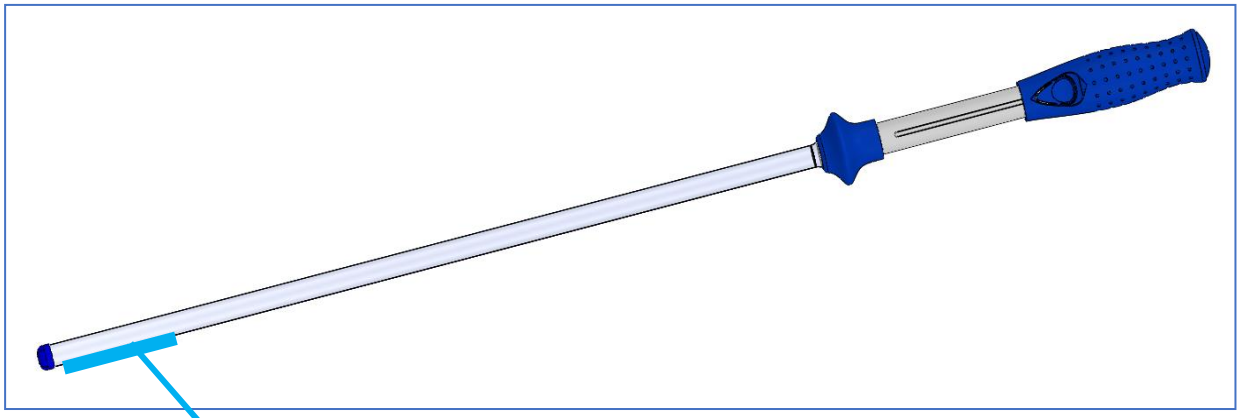

Figure 1: Introducer pre-loaded with the Colovac Device

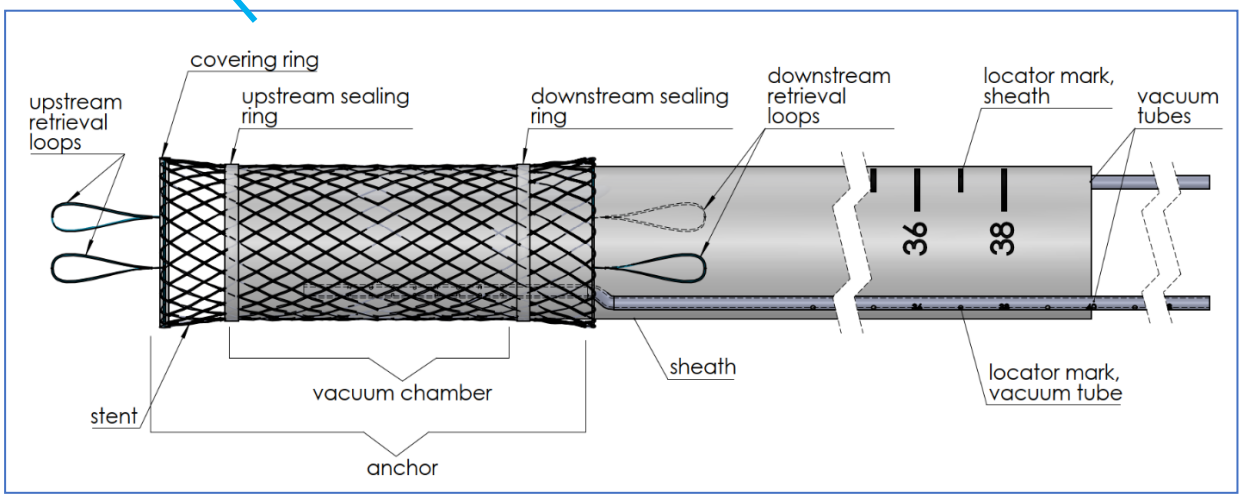

Figure 2: Colovac Device

As shown in Figure 2, the Colovac Device is composed of:

An anchor consisting of a covered double-stent assembly delimiting an air- and water-tight volume (i.e. vacuum chamber) in which a vacuum is pulled upon delivery in the colon through two vacuum tubes.

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 vacuum chamber is created in the area where the two stents overlap (in Figure 2, the stent overlap area coincides with the vacuum chamber). The layer made of the second stent material creates space that provides air channels to distribute the vacuum.

The upstream end of the vacuum tube, which is located within the vacuum chamber is multiperforated. The unperforated section of the vacuum tube passes through the downstream sealing ring and is long enough to protrude outside of the patient's anus and be attached to a standard, commercially available high vacuum drainage system (high volume vacuum vial) by a vacuum connector. The high-vacuum drainage system 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 Introducer (Figure 3) is a single use device, which is used to deliver the Colovac Device during a colectomy procedure, once the colorectal anastomosis is complete.

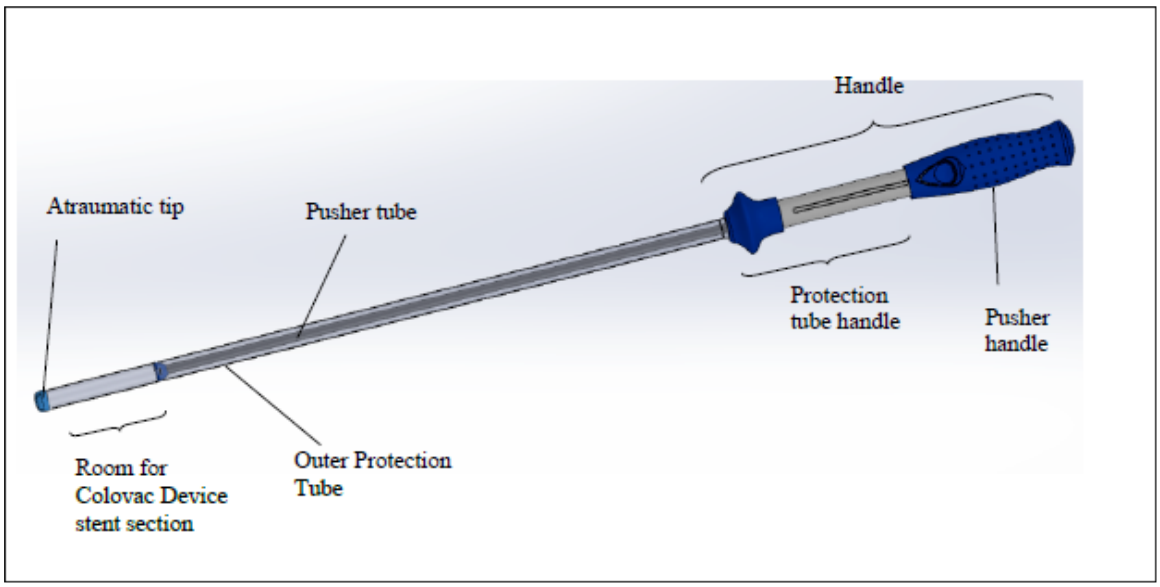

Figure 3: Introducer Internal View

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 upstream tip of the Introducer holds the stent section of the Colovac Device.

The Colovac Device is prepared with the stent and the sheath enclosed within the Outer Protection Tube. The stent is compressed in a radially retracted position for introduction. Initially compressed, the Colovac Device has a reduced diameter (16mm) to enable safe insertion and subsequent deployment into the GI tract. 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 in Figure 4, the Colovac device is designed with a 34 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 mm[31]. Furthermore, the colon diameter adapts to the stent diameter. 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.

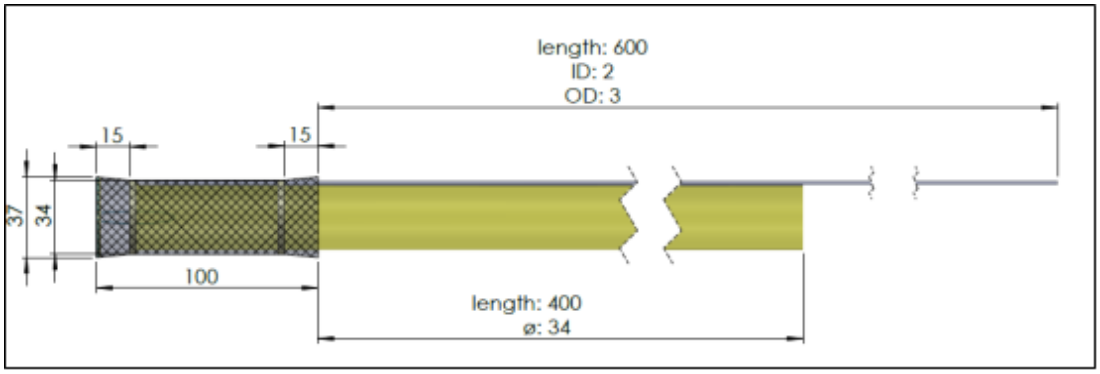

Figure 4: Colovac Dimensions

The Outer Protection Tube is a straight tubular external envelope that holds the anchor element (i.e. stent section) of the Colovac Device in a compressed state during the insertion procedure. The Pusher Tube is disposed axially inside the Outer Protection Tube, retaining the stent in place when the Outer Protection Tube is pulled back to release the device at its delivery site.

The Colovac Colorectal Anastomosis Protection Device is packaged in a sterile pouch fitted in a cardboard box together with the Instructions for Use (IFU), as shown in Figure 5.

Figure 5: Packaged example of Colovac Device

COLOVAC DEVICE IMPLANTATION PROCEDURE

Details of the Colovac Device implantation procedure are provided below. For complete instructions, please refer to the Colovac Colorectal Anastomosis Protection Device IFU provided in Appendix 1.

Prepare the Introducer and apply a generous amount of lubricant (refer to IFU for specific recommendations), a water-based lubricant inside the tip of the introducer so that it flows between the stent and the entire length of the introducer outer protection tube. Massage the stent to ensure that the stent is well lubricated and fully positioned within the Introducer outer protection tube. Apply lubricant to the outside of the Introducer outer protection tube.

Using the introducer handle, push the stent approximately 2mm out of the tulip using the handle as shown in 7. Release the lock button and guide the stent back into the outer sheath with fingers and the handle into the locked position before implantation. CAUTION - DO NOT continue holding down on the lock button, as handle pieces may separate. If handle pieces separate, DO NOT use the device.

Advance the Introducer through the anal orifice and gently route it to the delivery site.

At the point where the tip of the Introducer advances above the level of the sacral promontory, note the next visible locator mark on the Introducer outer protection tube at the level of the anus. Each locator mark represents a distance of 5 cm. Advance the Introducer at least 3 more locator marks to ensure the downstream part of the stent is placed above the top of the sacral promontory (shown in Figure 6). Visually or tactilely confirm the proper location of the Introducer above the top of the sacral promontory.

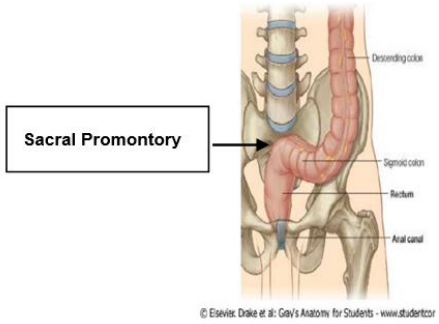

Figure 6: Landmark of Sacral Promontory

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Once proper location of the Introducer is confirmed, press the lock button on the downstream piece of the Introducer handle (see Figure 7) and start pulling back the blue upstream ring while keeping the downstream handle in place (Figure 8).

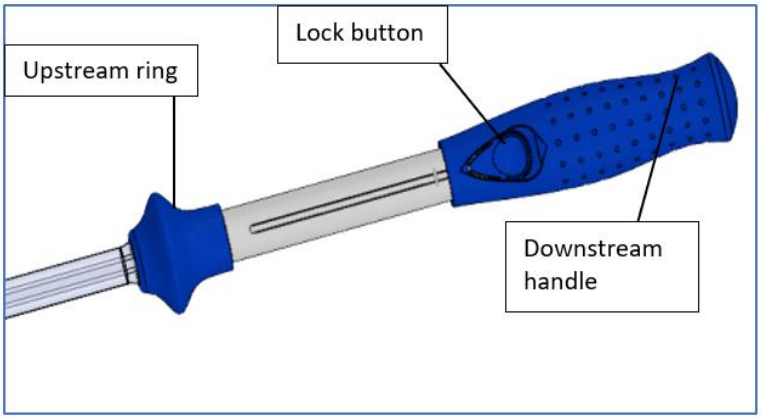

Figure 7: Introducer Handle

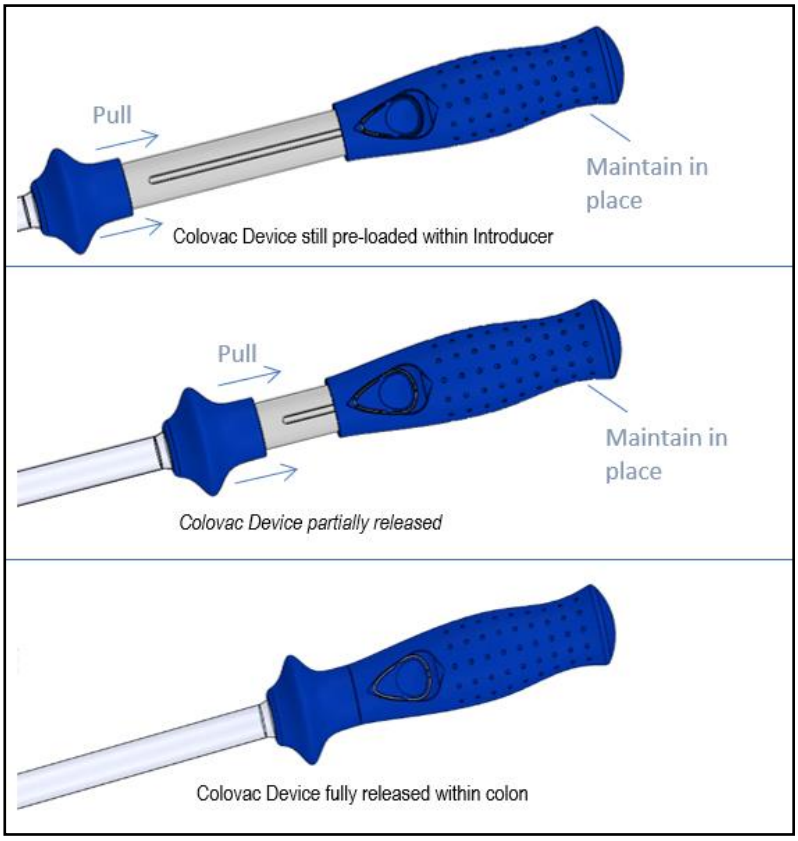

Figure 8: Introducer Handle During Placement of Stent

This action releases the stent section of the Colovac Device from the Introducer into the colon. Once the upstream ring has been pulled back completely so that the white section between the blue handle pieces is no longer visible (Figure 8), the stent section of the Colovac Device has been fully released.

Visually confirm that the Device is positioned above the top of the sacral promontory and verify that the stent has properly opened upon release from the Introducer. Gently remove the Introducer from the colon in the following steps.

Note: Check that the stent section of the Colovac Device stays in place during Introducer withdrawal. To prevent stent migration while removing the introducer, hold the stent in place by grasping its lower extremity using an atraumatic grasper, or manually in case of a laparotomy. While holding the handle in a fixed position (can be pressed on your leg or hip), cut the Introducer protection tube circumferentially above the upstream ring. Refer to the IFU for more details.

This stent is secured through the continuous application of a negative pressure, which is generated by means of a standard 510(k) cleared and CE marked high-vacuum drainage system. The vacuum

application on the Colovac Device should be started 2-3 min after placement of the Colovac Device once the device is fully expanded. Prepare the 600 ml high-vacuum drainage systems and remove the drainage systems from their sterile packaging. Two flexible vacuum tubes pass through the sealing ring inside the Vacuum Chamber. These flexible Vacuum Tubes are of sufficient length to pass beyond the anus and connect to the Vacuum Drainage Systems (**Figure 10**).

Cut about 1 cm off of the end of both Vacuum Tubes extending from the anus and rinse the cut ends (inside and outside) in isopropyl alcohol before attaching them to the SafeHeal Vacuum Connectors. Refer to the IFU for more details.

The resulting negative pressure inside the Vacuum Chamber achieves an anchoring effect by drawing the mucosal wall to the stent. The controlled anchoring is fully reversible without creating significant damage to the GI mucosa. The length of the sheath is such that the sheath covers the anastomosis from the anchoring position to beyond the anal sphincter. As means for monitoring sheath fluctuation and potential migration, the sheath of the Colovac Device is printed with marks in 1 cm increments.

Accessory Devices

The following accessories will be supplied to study sites:

SafeHeal Vacuum Connector
Vacuum drainage system, including vacuum drainage bottles and drainage line sets, from pfm Medical USA (ASEPT or JetVAC brands at US sites and ASEPT or Redon brands at OUS sites).
SafeHeal Vacuum Loss Alert System

SafeHeal Vacuum Connector

SafeHeal will provide the SafeHeal Vacuum Connector, a luer-lock connector, to attach the Colovac Device vacuum tubing to the vacuum drainage system.

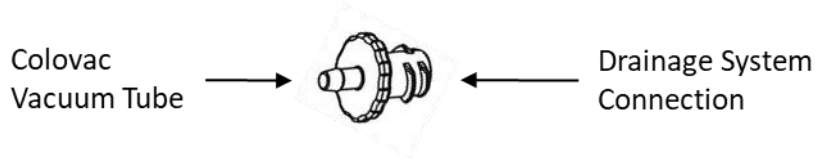

Figure 9: SafeHeal Vacuum Connector

Vacuum Drainage Systems

The Colovac Device is designed to be used in conjunction with standard CE or FDA-marked high-vacuum drainage systems with a volume of 600ml (Figure 10) from pfm Medical USA (ASEPT or JetVAC brands at US sites and ASEPT or Redon brands at OUS sites.

The vacuum drainage system is not part of the Colovac Anastomosis Protection Device and must be purchased separately. For the SAFE-2 clinical trial, the Sponsor will supply the vacuum drainage system to the investigator sites.

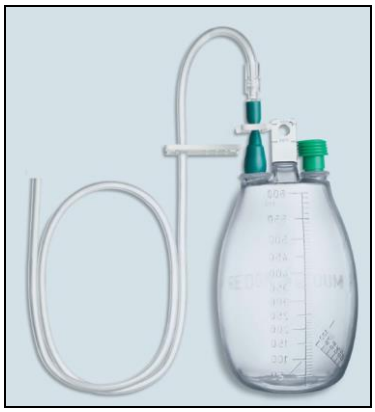

Figure 10: Vacuum Drainage System

Attach the vacuum tube to the vacuum connector and the vacuum connector to the PFM Asept Drainage Line Set and drain bottles.

SafeHeal Vacuum Loss Alert System

The Vacuum Loss Alert System (Figure 11) is a single-patient use, non-sterile unit used in conjunction with vacuum drainage system (as described above). The System attaches to the vacuum bottles and provides caregivers with visual and auditory alerts when a bottle reaches a low level of vacuum. The System is intended for use in conjunction with the existing visual bottle vacuum indicator to allow for continuous vacuum monitoring. The System is indicated for use during patient recovery in hospital/hospital-like environments (e.g., patient hospital rooms). Please refer to the Instructions for Use of the Colovac device and the Instructions for Use of the Vacuum Loss Alert System for instructions on how to attach the Vacuum Loss Alert System to the vacuum drainage system. Although the SafeHeal Vacuum Loss Alert System is not part of the Colovac Device, it will be supplied to sites.

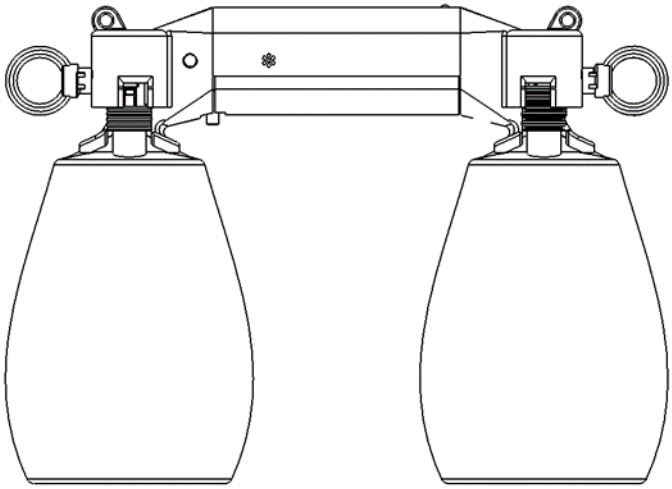

Figure 11: SafeHeal Vacuum Loss Alert System

Additional Device

The Hollister 9781 Horizontal Tube Attachment Device is not part of the Colovac Device and must be purchased separately. For the SAFE-2 clinical trial, the Sponsor will supply the Hollister 9781 Horizontal Tube Attachment Device to the investigator sites.

The vacuum drainage tubes are secured to the subject using an adhesive. To minimize subject discomfort due to tube movement, the Hollister 9781 Horizontal Tube Attachment Device (Figure **12**), a sterile, flexible support with adhesive backing, will be supplied to study sites.

Please refer to the Hollister 9781 Horizontal Tube Attachment Device **Instructions for Use for information on how to attach it to patient's skin.**

Figure 12**: Hollister 9781 Horizontal Tube Attachment Device**

STUDY DESIGN

OVERALL STUDY DESIGN

This is a pivotal, multicenter, prospective, randomized, open-label controlled trial. A total of 342 randomized subjects (171 investigational and 171 control subjects) will be enrolled at up to 15 US sites and up to 10 EU sites. Note that no site may enroll more than 20% of the total study enrollment without prior Sponsor approval. Subjects will be randomized into a control arm or a treatment arm (1:1 randomization) once all eligibility criteria have been met.

Control Arm – Stoma Pathway: Sphincter-preserving LAR and ostomy with stoma creation, followed by stoma closure within the next 12 months.

Treatment Arm – Colovac Pathway: Sphincter-preserving LAR with Colovac placement. Depending on the state of anastomotic healing at the end of the 10-day device implantation period, the index surgery is followed by either endoscopic device retrieval or endoscopic device retrieval plus ostomy with stoma creation surgery followed by stoma closure surgery within the next 12 months.

The study includes a run-in component that will include two non-randomized Colovac subjects at each US site. The IDE sample size will be increased for these subjects in the run-in cohort. In addition to the other eCRFs, the Usability Questionnaire eCRF will be completed for each run-in patient to assess any deployment challenges or technical difficulties, as well as to capture any adverse events that occur during Colovac implantation. Note that European sites with no experience implanting the Colovac device will enroll 2 subjects per site in a European run-in component. However, the IDE sample size will not be increased for these OUS subjects. Their results will be reported separately when the IDE results are reported.

Figure 13 below describes the patient management algorithm for both the control and the treatment arms.

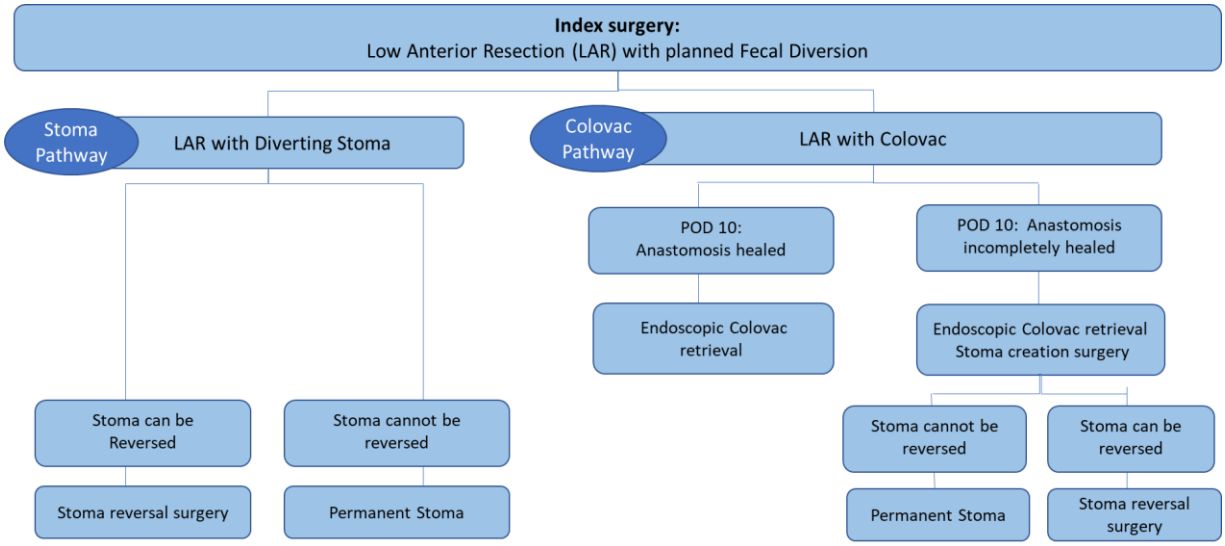

Figure 13: Description of the Two Patient Management Algorithms

STUDY OBJECTIVES

PRIMARY OBJECTIVES

The primary study objectives are

To assess the safety of the Colovac device by comparing the rate of major complications, as defined in the protocol;

To assess the effectiveness of the Colovac device in reducing the stoma creation rate.

SECONDARY OBJECTIVES

The secondary objectives of the investigation are:

To compare the cumulative length of hospital stay within 12 months post-discharge

To provide an additional assessment of product safety via the Comprehensive Classification Index (CCI)

To evaluate patient quality of life via the LARS Score within 12 Months

To evaluate patient quality of life via the EQ-5D-5L Quality of Life within 12 Months

To assess the performance of the Colovac device in diversion of fecal stream, avoidance of clinically significant and symptomatic AL, and avoidance of clinically significant migration

To evaluate diversion of fecal stream assessed by endoscopic evaluation before device removal

To evaluate the absence of clinically significant and symptomatic leak.

To evaluate avoidance of clinically significant migration

To evaluate the mucosal appearance (integrity of the anchoring site) and the integrity of the anastomosis after the device retrieval.

To assess the patient acceptance and tolerability of the device, during the Colovac Device implantation period

To assess the anastomosis at 6 and 12 months post-surgery.

To assess the integrity of the anchoring site at 6 and 12 months post-surgery

STUDY ENDPOINTS

PRIMARY SAFETY ENDPOINT

The primary safety endpoint is the rate of subjects with post-operative major complications within 12 months.

Major complications are defined as:
Index surgery-related, device-related (including implantation and retrieval), or ostomy-related (including creation and reversal) **and** Clavien-Dindo Severity[32]:

Grade II and re-admission to hospital is required for additional treatment* **or**

Grade III, IV or V

OR

- Patient safety risk leading to failure to reverse the stoma within 12 months**

*Additional treatment does not include administration of antiemetics, antipyretics, analgesics, diuretics and electrolytes and hospital stay does not include emergency room visits.

**Does not include failure to reverse stoma for reasons unrelated to patient safety.

The definition of major complications is intended to select only complications that do not respond to less complex treatments such as dietary change and administration of nominal drugs (antiemetics, antipyretics, analgesics, diuretics and electrolytes).

For example, a Grade II anastomotic complication, may be managed with prolongation of hospitalization or an emergency room visit for close monitoring or administration of antibiotics, and should not be considered a major complication. However, a Grade II complication that is recalcitrant to outpatient or emergency room treatment and requires re-hospitalization for administration of non-nominal drugs or other treatments, should rightly be considered a major complication.

As shown in Table 1, no Grade I and all Grades III, IV and V complications are major complications. Further, the only Grade II complications that are major complications are one that cannot be adequately treated in a clinic or emergency room and instead require re-admission to the hospital for administration of non-nominal drugs or other treatments.

Table 1: Explanation of Major Complications

Clavien-Dindo Severity	Explanation	Major Complication?
Grade I	All complications, regardless of hospitalization or treatment	No
Grade II	Complication resulting in a prolongation of the index hospitalization	No
Grade II	Complication resulting in an emergency room visit for administration of drugs / treatments without re-admission to the hospital	No
Grade II	Complication with an emergency room visit for administration of drugs / treatments without significant improvement of the clinical status of the patient, with re-admission to the hospital for further surveillance or administration of antiemetics, antipyretics, analgesics, diuretics and electrolytes	No
Grade II	Complication resulting in a re-admission to the hospital for further surveillance	No
Grade II	Complication resulting in a re-admission to the hospital for administration of drugs (other than antiemetics, antipyretics, analgesics, diuretics and electrolytes) or other additional treatment.	Yes
Grade III, IV, V	All complications	Yes
n/a	Complication that prevents ostomy reversal by 12 months	Yes

Three representative LAR-related adverse events (postoperative Ileus, small bowel obstruction and anastomotic complication) are listed in Table 2 to further illustrate which combinations of AE, treatment and Clavien-Dindo severity should be classified as major complications. For example, a postoperative ileus that resulted in a prolongation of the index hospitalization with insertion or re-insertion of NGT after surgery, and/or return to NPO status for nausea and/or vomiting is Grade 1 in severity and is not a major

complication. On the other hand, a postoperative ileus that resulted in a prolongation of the index hospitalization and required reoperation is Grade IIIb in severity and is a major complication.

Table 2: Examples of Representative LAR-Related AEs with Treatment and Major Complication Status

Adverse Event	Treatment	Clavien-Dindo Severity	Major Complication?
Postoperative Ileus / Small Bowel Obstruction	Resulted in a prolongation of the index hospitalization. Insertion or re-insertion of nasogastric tube (NGT) after surgery, and/or return to NPO status for nausea and/or vomiting.	Grade I or II	No
	Resulted in an emergency room visit without re-admission to the hospital	Grade I or II	No
	Resulted in a re-admission to the hospital – with or without any emergency room visit Required further surveillance, return to NPO	Grade I	No
	Resulted in a re-admission to the hospital – with or without any emergency room visit- Required insertion of an NGT and or administration of a non-nominal[1] drug	Grade II	Yes
	Resulted in a prolongation of the index hospitalization or a re-admission to the hospital Requiring reoperation.	Grade IIIb	Yes
Anastomotic Complication	Resulted in a prolongation of the index hospitalization. Required close monitoring of the patient for continued improvement or antibiotics administration	Grade I or II	No
	Resulted in an emergency visit. Required administration of antibiotics	Grade II	No
	Resulted in a re-admission to the hospital – with or without any emergency room visit- Required close monitoring of the patient for continued improvement	Grade I	No
	Resulted in a re-admission to the hospital – with or without any emergency room visit- Required administration of antibiotics	Grade II	Yes

Adverse Event	Treatment	Clavien-Dindo Severity	Major Complication?
	Resulted in a prolongation of the index hospitalization or re-admission to the hospital Required re operation	Grade III or IV	Yes

[1]Nominal drugs: antiemetics, antipyretics, analgesics, diuretics and electrolytes

Two representative ostomy-related adverse events (high stoma output/dehydration and parastomal hernia / hernia at the ileostomy site complication) are listed in Table 3 to further illustrate which combinations of AE, treatment and Clavien-Dindo severity should be classified as major complications. For example, a high stoma output/dehydration that resulted in a prolongation of the index hospitalization with excessive loss of body fluids necessitating IV repletion or stoma care/stoma replacement is Grade 1 in severity and is not a major complication. On the other hand, a high stoma output/dehydration that resulted in a re-admission to the hospital and administration of a non-nominal drug is Grade II in severity and is a major complication.

Table 3: Examples of Representative Ostomy-Related AEs with Treatment and Major Complication Status

Adverse Event	Treatment	Clavien-Dindo Severity	Major Complication?
High stoma output/ Dehydration	Resulted in a prolongation of the index hospitalization. Excessive loss of body fluids necessitating IV repletion or stoma care/stoma replacement	Grade I	No
	Resulted in a re-admission to the hospital. Required administration of non-nominal[1] drug	Grade II	Yes
	Resulted in a prolongation to the hospitalization Required reoperation	Grade IIIa or IIIb	Yes
Parastomal Hernia/ Hernia at the ileostomy site	Resulted in a prolongation of the index hospitalization. Required conservative management	Grade I	No
	Resulted in an emergency room visit without re-admission to the hospital	Grade I or II	No
	Resulted in a re-admission to the hospital. Required conservative management	Grade I	No

Adverse Event	Treatment	Clavien-Dindo Severity	Major Complication?
	Resulted in a re-admission to the hospital. Required reoperation	Grade IIIa or IIIb	Yes

[1]Nominal drugs: antiemetics, antipyretics, analgesics, diuretics and electrolytes

Additionally, the CEC will verify that major complications with Grade II severity are eligible for inclusion as major complications based on the additional requirements. Similarly, the CEC will verify that failure to reverse the stoma within 12 months was based on an adverse event or other patient safety concern rather than patient preference or other reason unrelated to patient safety.

The Clavien-Dindo severity classification, the basis for the severity stratifications of the complications, is included in Section 0. Adverse events will also be classified by seriousness based on the definition provided below in Section 0.

Note that all adverse events will be collected and presented in the clinical study report. To provide a fair comparison of the two treatment pathways, the following planned procedures for both pathways will not be considered a safety event within the Primary Safety Endpoint:

Stoma reversal surgery
Endoscopic Colovac retrieval
Stoma creation surgery for incomplete anastomotic healing

However, all AEs related to these procedures that meet the criteria for Major Complications will be included in the Primary Safety Endpoint analysis. These procedures are summarized below in Figure 14.

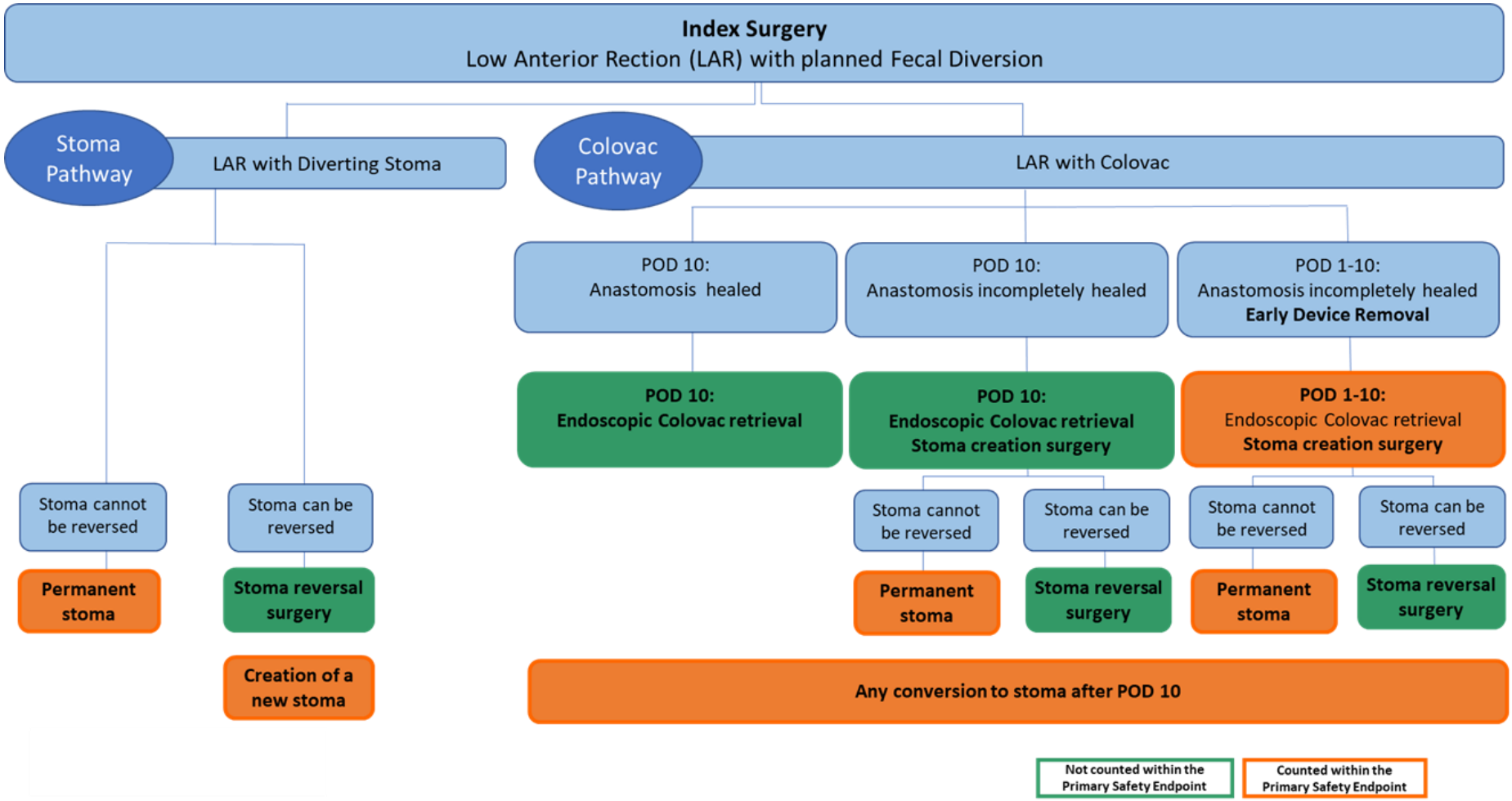

Figure 14: Description of Procedures and Alignment to the Primary Safety Endpoint

PRIMARY EFFECTIVENESS ENDPOINT FOR COLOVAC ARM

The primary effectiveness endpoint assessed for all subjects in the Colovac arm at 12 months is a clinically meaningful reduction in stoma creation rate.

Avoidance of stoma creation is an objective, standardized primary effectiveness endpoint that ensures that all cases (whether a result of the procedure, the device or the patient's poor healing) of failure to divert the fecal stream, anastomotic leak, and migration that resulted in a stoma conversion are counted as endpoint failures.

The endpoint will be considered a failure if the subject requires stoma creation. This endpoint addresses the following:

Diversion of the fecal stream from the anastomosis site:

Failure to divert the fecal stream from the anastomosis (whether a result of the procedure, the device, or the patient's poor healing) which results in stoma creation within 12 months of the index surgery will be counted as endpoint failures.

In addition, all anastomotic leaks (ALs) (including incomplete healing at Day 10 not related to failure to divert the fecal stream) that result in stoma creation for any reason within 12 months of the index surgery and will be counted as endpoint failures

Device migration

All device migrations that result in stoma creation will be counted as endpoint failures.

Primary Effectiveness Endpoint Success

To be considered a primary effectiveness success, the subject must have no stoma creation, regardless of the reason, within 12 Months of the index surgery. Note: Fecal contamination which results in stoma creation within 12 months of the index surgery (whether a result of the procedure, the device or the patient's poor healing) will be counted as endpoint failures.

PERFORMANCE GOAL FOR PRIMARY EFFECTIVENESS

Study success will be defined as a clinically meaningful stoma reduction rate in the Colovac patients AND statistical non-inferiority on the primary safety endpoint (Colovac vs. Control). A benefit-risk assessment of all the clinical data will be performed to determine the ostomy reduction rate that balances the risk that device use may pose. This ostomy reduction rate will be considered clinically meaningful and provide the basis for the actual performance goal for this endpoint. Details of the benefit-risk assessment are provided in Section 0.

SECONDARY AND EXPLORATORY ENDPOINTS

Secondary Effectiveness Endpoints

For Comparison between the Colovac and Control Arms

- - Cumulative Length of Hospital Stay through 12 Months post-discharge: Total length of hospital stay (in days) through the 12-month visit will be compared between the two study arms.

- Comprehensive Classification Index (CCI)[33]: The CCI is the sum of all AEs, weighted by their severity. The CCI will be collected and compared between the treatment group and the control group. The CCI includes all postoperative complications and thus, is more comprehensive and more sensitive than other safety endpoints. The CCI is calculated on the basis of tabulated complications classified according to the Clavien-Dindo classification.

- LARS Quality of Life: The Low Anterior Resection Syndrome (LARS) QOL at 6 months post-index surgery will be compared between study arms using the LARS questionnaire. The questionnaire consists of five items that include: frequent bowel movements, gas, and fecal incontinence, fragmentation, and urgency. The LARS score ranges from 0-42, where 0 is no symptoms and 42 is all symptoms at least once per week. The LARS score at 6 months post-index surgery will be compared between the two treatment arms as a numeric measure. Note that as the LARS questionnaire cannot be completed by subjects in the Control arm until after ostomy reversal, if a Control subject does not have a score at 6 months, the score at the next closest time point will be used.

- EQ-5D-5L Quality of Life (QOL): Patient QOL at 1 month post-index surgery will be compared between study arms using EQ-5D-5L questionnaire. The EQ-5D-5L comprises the following five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression. Each dimension has five response levels: no problems, slight problems, moderate problems, severe problems, unable to/extreme problems. Additionally, the EQ Visual Analogue Scale VAS records the respondent's overall current

health on a visual analogue scale where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'.

- Assessment of anastomosis at 6 and 12-months post-surgery: A sigmoidoscopic evaluation of the anastomosis will be performed to assess the integrity of the anastomosis at the 6 and 12-month visits.

For Colovac Treated Patients Only

The secondary composite effectiveness endpoint assessed for all subjects in the Colovac arm at Day 10 is:
Diversion of fecal contents from the anastomosis site confirmed by endoscopic evaluation for the absence of feces between the sheath and the colonic wall AND the absence of clinically significant and symptomatic AL; AND
Absence of clinically significant migration

The composite effectiveness endpoint for the Colovac-treated patients is a measure of subject-level success that will be assessed on all subjects in the Colovac arm who have the device implanted until Day 10. Additionally, all subjects who have the device removed before Day 10 due to a device-related reason will be included in the assessment as failures. Subjects who have the device removed before Day 10 due to a non-device related reason will be included in the assessment as missing.

Diversion of fecal stream from the anastomosis will be confirmed using the Boston Bowel Preparation Scale (BBPS) score (BBPS = 3). To standardize this assessment, photographs of the anastomosis site will be taken during the endoscopic procedure following device removal and the review of the endoscopic photographs will be entrusted to the Clinical Evaluation Committee for independent review of the presence of feces using the Boston Bowel Preparation Score (BBPS). A BBPS ≠ 3 will be considered a failure.

ALs classified as ISREC severe Grade B and Grade C will be considered clinically significant and symptomatic. The ISREC grades are defined in Section 6.3.5.

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

Migration of entire stent 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.

If the entire stent is below the sacral promontory, the physician should consider converting the patient to the standard of care ostomy within 24 hours.

A treatment algorithm flowchart detailing the treatment pathways is provided below in Figure 15.

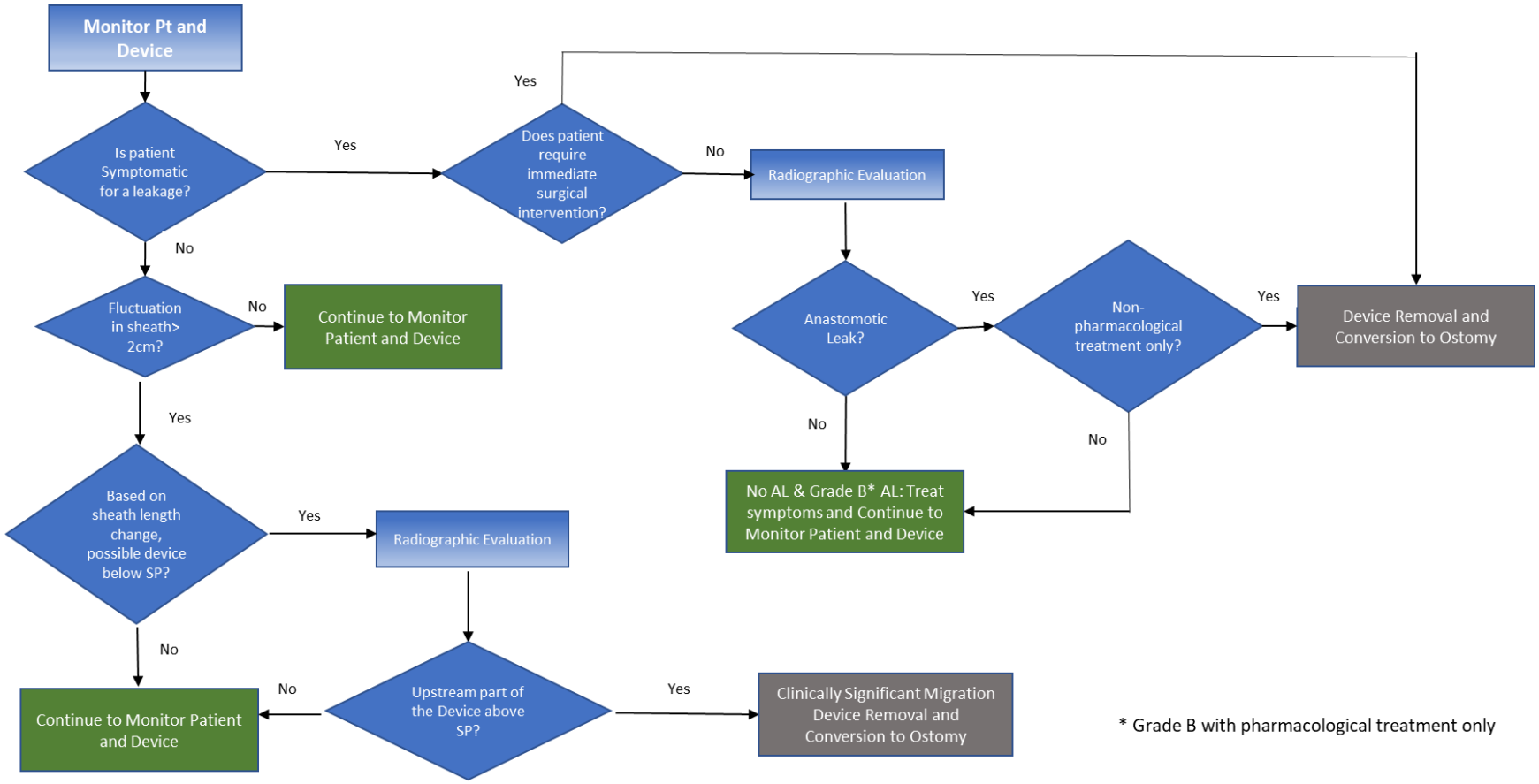

Figure 15: : Colovac Treatment Algorithm Flowchart

Figure 16 illustrates the decision pathways for determination of the secondary composite effectiveness endpoint.

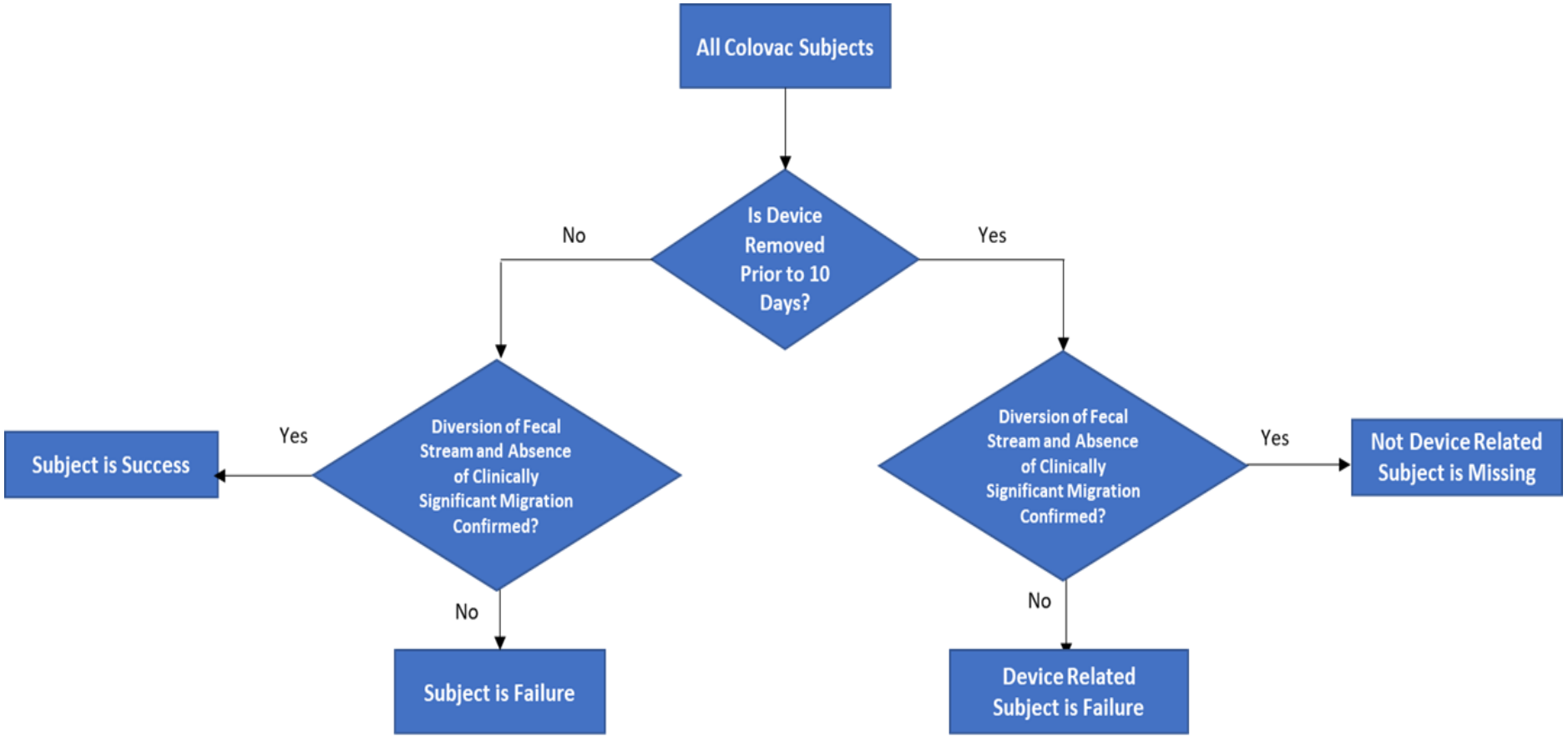

Figure 16: Secondary Composite Effectiveness Endpoint Determination

As the secondary effectiveness endpoint cannot be assessed in the control group, the control group cannot be used as comparator to determine success. Thus, the secondary composite effectiveness endpoint will be compared to a performance goal. Details on the determination of the performance goal will be provided in a separate Statistical Analysis Plan.

Diversion of fecal stream from the anastomosis site confirmed by endoscopic evaluation for the absence of feces between the sheath and the colonic wall

Absence of clinically significant and symptomatic leak

Absence of clinically significant migration

Elective Ostomy Conversion Rate through 12 Months: The rate of elective ostomy creation through the 12-month visit.

- Assessment of mucosal appearance and anastomosis after device retrieval:
  - Mucosal appearance at anchoring site classified as Bleeding, Ulcerated, Perforated.
  - Assessment of anastomosis after device retrieval per the clinician's standard practice, classified as Normal or Presence of Leakage

Patient acceptance and tolerability, including:
- Usage of external sheath and external vacuum tubes through the anus (rated on a scale from 1 full acceptance to 5 no acceptance)
- Presence of vacuum system (rated on a scale from 1 full acceptance to 5 no acceptance)

Assessment of anchoring site at 6 and 12 months post-surgery:
- Mucosal appearance at anchoring site classified as Bleeding, Ulcerated, Perforated.

Exploratory Endpoints

Overall Morbidity: All reported adverse events (AEs) will be collected and compared between the treatment group and the control group.

Assessment of anastomosis integrity on Day 9 (+3 days) will be compared between the two study arms. Note that this assessment will occur prior to device retrieval for subjects in the Colovac Arm. A double contrast CT Scan with a slice thickness of 1 mm in acquisition and 2 mm in reconstruction will

be performed to check for anastomotic integrity. Anastomosis will be classified as Normal, Presence of Leakage, Presence of Dehiscence.
Subgroup analyses of the primary and secondary effectiveness endpoints by Neoadjuvant chemoradiation, Type 2 Diabetes Mellitus, Age, Gender, BMI, Colon diameter, surgical approach and anastomosis location.

ASSESSMENT OF ANASTOMOTIC LEAKAGE

As anastomotic leak (AL) represent the most common AE related to LAR surgeries, the following section describes how those complications will be assessed throughout this SAFE-2 Study.

For harmonization between study centers, the clinical significance of all ALs will be assessed using a combination of a standard classification system of AL, International Study Group of Rectal Cancer (ISREC) grading system for the management of colorectal anastomotic leaks[34,35] and the Clavien-Dindo classification[13,14]. This is consistent with the definition of major complications.

The ISREC grading system classifies ALs into one of three grades based on severity and required treatment. The ISREC grades are defined as follows:[36]

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.

The Clavien-Dindo (CL) classification is shown in Table 4.

Table 4: 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, analgesics, 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

As shown in Table 5, by definition, all ISREC Grade A ALs are CL Grade 0 or I severity, all ISREC Grade B ALs are CL Grade II or IIIa severity, and all ISREC Grade C AL are CL Grade IIIb, IVa, IVb or V in severity. Consistent with the definition of major complications, the CL Grade II is divided into those with and without re-hospitalization.

All ISREC Grade B ALs that are CL Grade II severity with re-hospitalization or CL Grade IIIa severity, and all ISREC Grade C ALs (CL Grades IIIb, IVa, IVb and V severity) will be considered CSS AL. The only ISREC Grade B ALs that would be excluded from the CSS AL definition would be those that are CL Grade II severity without re-hospitalization.

Table 5: Assessment of CSS AL

ISREC AL Grade	CL Severity Grade	CSS AL?
Grade A	0, I	No

ISREC AL Grade	CL Severity Grade	CSS AL?
Grade B		
Requires pharmaceutical treatment only (e.g., antibiotics, analgesics)	II without re-hospitalization	No
Requires pharmaceutical treatment only (e.g., antibiotics, analgesics)	II with re-hospitalization	Yes
Requires non-pharmaceutical treatment (e.g., percutaneous drain)	IIIa	Yes
Grade C	IIIb, IVa, IVb, V	Yes

All ALs will be reported as adverse events and rates will be compared between the Colovac and Control groups. Grade B ALs that require re-hospitalization and/or require non-pharmaceutical treatment are considered “severe.”

Severe Grade B and Grade C AEs will be considered clinically significant and symptomatic.

To determine device relatedness of clinically significant and symptomatic AL, assessments will be performed at the time of intervention and device removal to determine if the device was effective at diverting the fecal stream (non-device related removal) or not (device-related removal).

Device relatedness for AL will be determined using the same diversion of fecal matter and migration criteria as the primary effectiveness endpoint:

Diversion of fecal stream from the anastomosis site confirmed by absence of feces at the anastomosis site confirmed by endoscopic evaluation between the sheath and the colonic wall performed before the device is removed (i.e. BBPS=3); AND
Absence of clinically significant migration

However, in rare cases of severe clinically significant and symptomatic AL (peritonitis) when a device is removed prior to Day 10, the subject may require emergent, surgical treatment. In this case, as the priority is to quickly treat the patient, the priority will be given to the examination and washout of the anastomosis, abdomen and pelvis to determine the extent of the infection and the necessary intervention. The retrieval of the device will be considered as one of the last tasks, once the patient is

stabilized. Thus, as the anastomosis will have been cleansed at the time of the endoscopic removal of the device, it will not always be possible to confirm diversion of the fecal stream by endoscopic evaluation. In these rare cases, an alternative method to confirm the diversion of fecal stream and allow the device effectiveness to be determined, the absence of fecal peritonitis, will be assessed.

As shown in Figure 17, all AL in the Colovac group will be assessed for relationship to the device and inclusion in the primary safety endpoint as a major complication. Similarly, as shown in Figure 18, all AL in the Standard of Care (Control) group will be assessed for inclusion in the primary safety endpoint as a major complication. Note that all AL complications will be included in the AE summary tables.

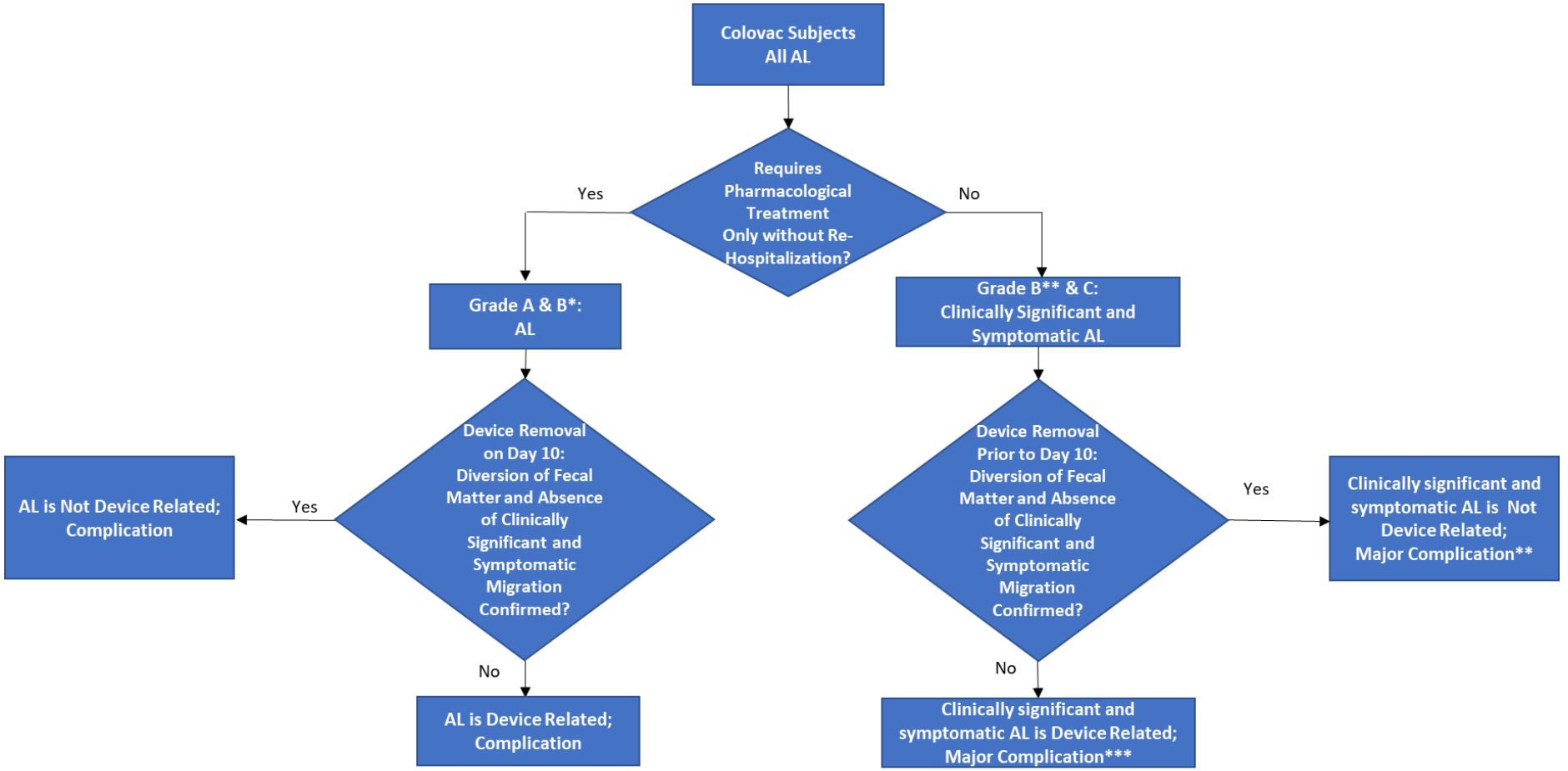

Figure 17: Anastomotic Leakage in Colovac Group by Grade, Device Relationship and Type of Complication

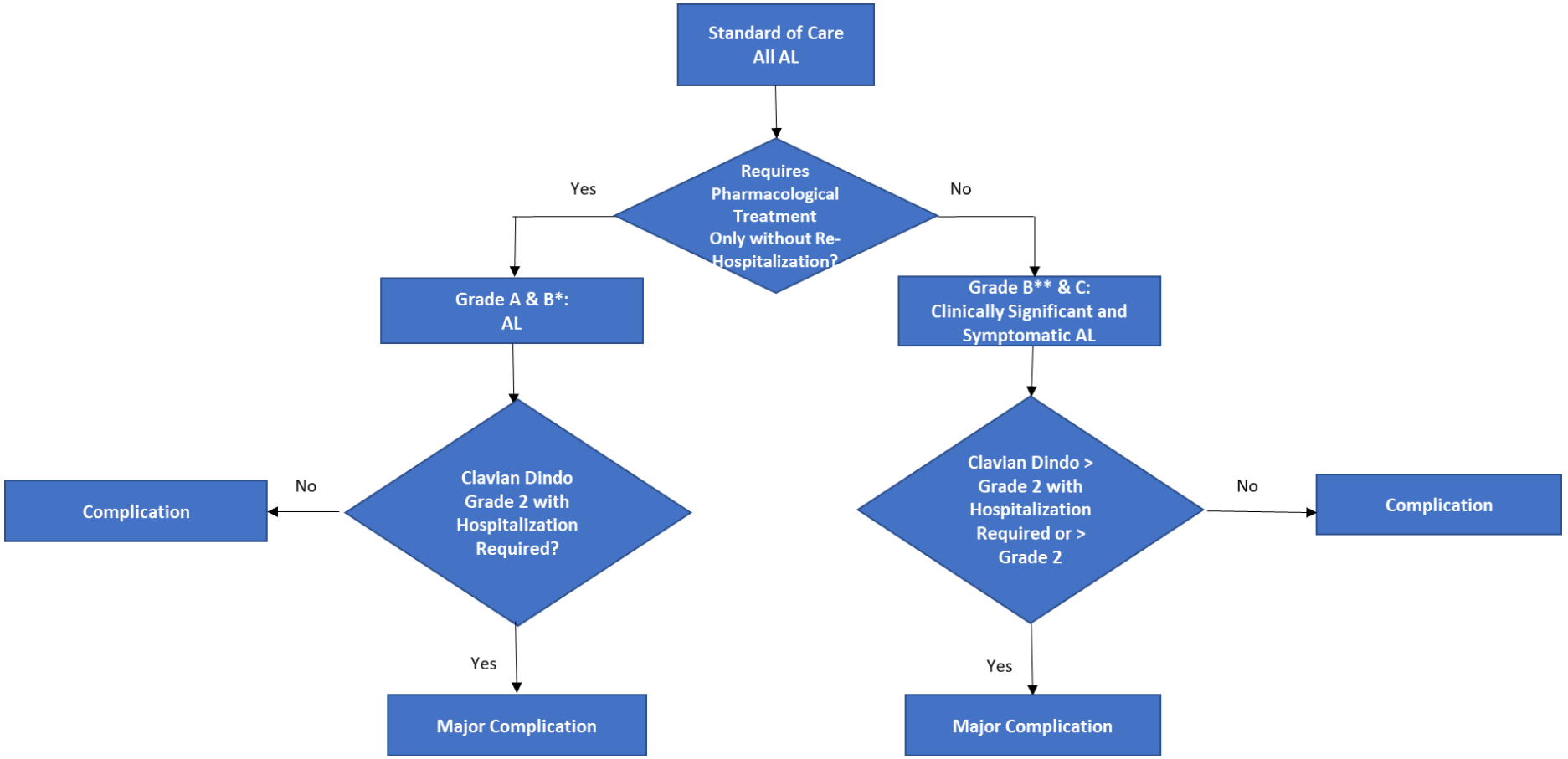

Figure 18: Anastomotic Leakage in Standard of Care Group by Grade and Type of Complication

STUDY POPULATION

All subjects will require low anterior colorectal resection for colorectal cancer with a planned diverting loop ileostomy. Additionally, subjects must meet all of the inclusion and none of the exclusion criteria to be enrolled in the study. A maximum of 30 non-randomized subjects (two subjects at each US site) will be enrolled in the run-in component of the study. A total of 342 subjects (171 in the control arm and 171 in the Colovac arm) will be enrolled in the randomized component of the study. At least 50% of the randomized subjects will be enrolled at US sites.

Note that European sites with no experience implanting the Colovac device will enroll 2 subjects per site in a European run-in component. However, the IDE sample size will not be increased for these OUS subjects. Their results will be reported separately when the IDE results are reported.

INCLUSION CRITERIA

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

1. Adult patients (greater than 18 years of age)
2. Eligible to undergo open or minimally invasive sphincter-preserving lower anterior resection (anastomosis within 10 cm of the anal verge) with planned diverting loop ileostomy for malignant indication, assessed by a multi-disciplinary team.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status[37] ≤ 2
4. Willing 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:

<u>Preoperative</u>

History of left colitis

Known allergy to nickel or other components of the Colovac kit

Pregnant or nursing female subject

Concomitant major surgical procedure in combination with Colorectal resection (e.g. hepatectomy)

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:

COVID-19 positive (active infection) based on test within 48 hours prior to surgery

Immunodeficiency (CD4+ count < 500 mm^3)

Systemic steroid therapy within the past 6 months

Systemic infection at the time of surgery or requiring systemic antimicrobial therapy up to 1 week before surgery

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

Diagnosis of bowel obstruction, bowel strangulation, peritonitis, bowel perforation, intraabdominal infection, ischemic bowel, carcinomatosis

Fecal incontinence, involvement of sphincter by the neoplastic disease or evidence of extensive local disease in the pelvis seen on pre-operative imaging

Severe Malnutrition defined as ≥ 10% weight loss within 3 months prior to enrollment.

The subject is currently participating in another investigational drug or device study

Intraoperative

Occurrence of any of the following during the colorectal surgery:

Blood loss (>750 cc)

Blood transfusion

Any new sign of ischemia

Positive air leak test – requiring re intervention on the anastomosis

Inadequate bowel preparation

Anastomosis location greater than 10 cm from the anal verge

Other intra-operative risks that preclude the subject from undergoing the procedure with the investigational device

STUDY PROCEDURES

Prior to randomization, the study procedures are the same for all subjects. Following randomization, the study procedures vary depending on whether the subject is assigned to the Control or Treatment Arm.

STUDY PROCEDURES BEFORE RANDOMIZATION

The schedule of study procedures before randomization are shown in Table 4 and the procedures are described below.

Table 4: Study Procedures Before Randomization

Procedure	Pre-Operative -Day -1 (-44 days)	Intraoperative (Index Surgery) Day 0
Informed Consent Signed	X	
Medical Billing Release Form*	X	
Screening/Preliminary Eligibility Determination	X	
Medical History and Physical Examination	X	
EQ5D QOL	X	
LARS QOL	X	
Low Anterior Resection Procedure (Index Surgery)		X

Procedure	Pre-Operative -Day -1 (-44 days)	Intraoperative (Index Surgery) Day 0
Surgery eCRF		X
Final (Intraoperative) Eligibility Determination		X
Screen Failure or Randomization		X

*Optional collection of financial information related to costs of medical treatment for future use outside this IDE in a health economics study.

Informed Consent:

Potential study participants are patients scheduled to undergo sphincter-preserving LAR with a planned diverting ostomy will be approached about study participation. The investigator or designated member of research staff will review the study and its risks and potential benefits with the patient, and answer all of the patient's questions regarding study participation. Interested patients will be provided a copy of the study information sheet and informed consent form and will be allowed adequate time to review it and, if desired, discuss with others.

If the patient agrees to take part in the study, the Investigator or a designated member of the site staff will obtain written informed consent.

Medical Billing Release Form:

US patients who sign the informed consent form will be asked to sign a medical billing release form to allow the release of financial information relating to the cost of any trial-related procedures and hospitalizations that occur during their participation in the SAFE-2 trial. This information will be collected for use outside of this IDE study in a future health economics study. Refusal to release medical billing information will have no impact on participation in the IDE.

Screening/Preliminary Eligibility Determination

During screening, if all inclusion criteria and no preoperative exclusion criteria are met, the subject will be considered for enrollment in the study. Note that the intraoperative exclusion criteria cannot be evaluated until the colon resection procedure (index surgery) is complete. At that time, a final determination of eligibility will be made.

Preoperative Assessments

The following preoperative assessments will be performed prior to the index surgery

- Medical history and physical examination to record demographics, tumor characteristics and related treatment
- Quality of Life scores

EQ-5D-5L: The EQ-5D-5L comprises the following five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression. Each dimension has five response levels: no problems, slight problems, moderate problems, severe problems, unable to/extreme problems. Additionally, the EQ VAS records the respondent's overall current health on a visual analogue scale where the endpoints are labelled "The best health you can imagine" and "The worst health you can imagine."

LARS Score – Low anterior colon resection is associated with bowel dysfunction, which negatively affects the patient's quality of life (QOL). Low Anterior Resection Syndrome (LARS) is characterized by high frequency of bowel movements, clustering, incomplete evacuation, diarrhea, incontinence for flatus and stool, urgency, and bowel movements at night. The severity of LARS can be measured with LARS score, a five-item instrument that consists of frequent bowel movements, gas incontinence, fecal incontinence, fragmentation, and urgency. The LARS score ranges from 0-42, where 0 is no symptoms and 42 is all symptoms at least once per week.

Low Anterior Resection Surgery:

The Low Anterior Resection surgery and creation of the anastomosis will be performed as per standard of care.

Final Eligibility per Intraoperative Exclusion Criteria:

If Exclusion Criterion 7 is met, the patient will be considered a screen failure.

Exclusion Criterion 7
Occurrence of any of the following during the colorectal surgery:
Blood loss (>750 cc)
Blood transfusion
Any new sign of ischemia
Positive air leak test – requiring re-intervention on the anastomosis
Anastomosis location is greater than 10 cm from the anal verge
Other intra-operative risks that preclude the subject from undergoing the procedure with the investigational device

Enrollment/Randomization:

If no intraoperative exclusion criteria are met, the subject will be enrolled in either the non-randomized run-in component or the randomized component of the study.

Prior to enrolling subjects in the randomized component of the study, the PI at each US site will implant the Colovac device in two non-randomized subjects. These subjects will be included in the run-in component of the study. During these run-in implantations, the PI will be proctored by a qualified member of the SafeHeal staff or representative to ensure safe and accurate deployment of the device.

Additionally, the Usability Questionnaire eCRF will be completed for each run-in patient to assess any implantation challenges or technical difficulties, as well as to capture any adverse events that occur during Colovac implantation. This run-in component of the study will include a maximum of 30 non-randomized subjects (2 subjects per site) from up to 15 US sites. Other than the mandatory proctoring during implantation and completion of the Usability eCRF, the run-in subjects will undergo the same treatment, examinations and procedures as the other Colovac subjects. However, the non-randomized run-in subjects will be analyzed separately from the randomized subjects.

Note that European sites with no experience implanting the Colovac device will enroll 2 subjects per site in a European run-in component. However, the IDE sample size will not be increased for these OUS subjects as they will not be included in the randomized cohort. Their results will be reported separately when the IDE results are reported.

After implanting two subjects in the run-in component, investigators will enroll subjects in the randomized component of the study.

If the site has completed enrollment in the run-in component, randomization will be performed to determine if the surgery will continue with an ostomy with stoma creation procedure (Control Arm) or if a Colovac device (Treatment Arm) will be inserted.

If a subject is randomized to the Control Arm (ostomy with stoma creation), the procedures listed in Section 0.will be followed. If a subject is randomized to the Treatment Arm (Colovac device), the procedures listed in Section 0 will be followed.

STUDY PROCEDURES AFTER RANDOMIZATION FOR A PATIENT IN THE CONTROL ARM / STOMA PATHWAY

The schedule of study procedures after randomization for a subject enrolled in the Control Arm are shown in Table 5 and the procedures are described below.

Table 5: Schedule of Study Procedures: Control Arm

Procedure	Surgery Day 0	Hospital Day 1- 5* Daily	Follow-up Day 9 (+3 days)	1 Month (±14 days)	3 Months (±14 days)	6 Months (±30 days)	9 Months (±30 days)	12 Months (±45 days)	If/when applicable
Ostomy Creation	X								
Daily Clinical Eval		X							
CRP		X**							
WBC, Hemoglobin				X	X	X	X	X	X
Contrast CT Scan of Anastomosis			X						
Anastomotic Test eCRF			X						
EQ5D QOL			X	X	X	X	X	X	
LARS QOL***				X	X	X	X	X	
Sigmoidoscopic Evaluation of Anastomosis						X		X	

Procedure	Surgery Day 0	Hospital Day 1- 5* Daily	Follow-up Day 9 (+3 days)	1 Month (±14 days)	3 Months (±14 days)	6 Months (±30 days)	9 Months (±30 days)	12 Months (±45 days)	If/when applicable
AEs	X	X	X	X	X	X	X	X	X****
Ostomy Reversal									X

*The actual length of hospitalization will vary based on individual patient factors. Daily follow-up will be performed as long as the subject is hospitalized.
**Starting on Day 2, CRP will be tested every 2 days during hospitalization
***LARS QOL will only be collected at follow-up visits after ostomy reversal
****AEs related to the stoma reversal procedure will be collected

Day 0 – Ostomy with Stoma Creation:

The ostomy with stoma creation will be performed per standard of care. Any AEs that occur during the procedure will be recorded on the AE eCRF.

Hospitalization Period Day 1 – Day 5

Subjects will be hospitalized for approximately 5 days following the index procedure and ostomy creation. However, the actual length of hospitalization will vary based on individual patient factors. Although the hospitalization period in Table 5 is Day 1 to Day 5, this is intended as an example only. Daily clinical follow-up will be performed as long as the subject is actually hospitalized.

Daily clinical follow-up per standard of care: The patient management will be performed per standard of care until the patient is discharged from hospital

CRP test every 2 days during hospitalization (starting on Day 2)

Any AEs that occur will be recorded on the AE eCRF.

Post-operative Day 9: CT Scan:

A double contrast (rectal and IV) CT Scan with 1mm thick slices for acquisition and 2 mm thick slices for reconstruction will be performed at Day 9 (+3 days) post index. Images will be recorded and analyzed to determine the presence or absence of leak and the description of the leak (if applicable). Information will be reported in the eCRF. Any AEs that have occurred since the last daily visit during the hospitalization period will be recorded on the AE eCRF.

Follow-up Period:

Patient management will be performed as per standard of care until the end of the follow up period. The stoma reversal surgery is planned if and when applicable.

Study follow up visits are planned at the following intervals after the index surgery:

1 Month (+/- 14 days)

3 Months (+/- 14 days) – can be conducted by telephone

6 Months (+/- 30 days)

9 Months (+/- 30 days) – can be conducted by telephone

12 Months (+/- 45 days)

* The 3 and 9-month visits may be conducted over the phone if these visits are not part of the investigator's standard of care.

At each visit, the EQ-5D-5L quality of life questionnaire will be completed by the subject and WBC and hemoglobin will be tested.

At each visit following ostomy reversal, the LARS quality of life questionnaire will be completed by the subject.

At the 6 and 12-month visits, a sigmoidoscopic evaluation of the anastomosis will be performed to assess the anastomosis.

Any AEs that the subject has experienced since the previous visit or phone call will be recorded on the AE eCRF.

Ostomy Reversal Procedure:

If the ostomy is reversed during the 12 month follow-up period of the study, details of the procedure and any related adverse events will be collected.

STUDY PROCEDURES AFTER RANDOMIZATION FOR A PATIENT INPLANTED WITH COLOVAC DEVICE

The schedule of study procedures for a patient in the randomized the Treatment Arm / Colovac Pathway or in the non-randomized Run-In Component are shown in Table 6 and the procedures are described below.

Table 6: Schedule of Study Procedures: Colovac Arm

		Hospitalization			Follow-up					
Procedure	**Surgery Day 0**	**Day 1- 8 Daily**	**Day 9 (+3 days)**	**Day 10 (-1/+2 days)**	**1 Month (±14 days)**	**3 Months (±14 days)**	**6 Months (±30 days)**	**9 Months (±30 days)**	**12 Months (±45 days)**	**If/when applicable**
Colovac Insertion	**X**									
Usability Questionnaire	**X***									
Device Position X-ray	**X****	**X****	**X****							
Daily Clinical Evaluation		**X**	**X**							

Procedure	Surgery Day 0	Hospitalization			Follow-up					
		Day 1- 8 Daily	Day 9 (+3 days)	Day 10 (-1/+2 days)	1 Month (±14 days)	3 Months (±14 days)	6 Months (±30 days)	9 Months (±30 days)	12 Months (±45 days)	If/when applicable
CRP		X***								
WBC, Hemoglobin					X	X	X	X	X	
Daily Study Evaluation		X	X							
Trim Sheath		Day 2 only								
Contrast CT Scan of Anastomosis			X							
Endoscopic Evaluation of Colon (BBPS score)				X†						
EQ5D QOL			X		X	X	X	X	X	
LARS QOL‡			X		X	X	X	X	X	
Colovac Retrieval				X						
Conversion to Ostomy										X
Endoscopic Examination of Mucosa Post-retrieval				X						
Evaluation of Anastomosis Post-retrieval				X						
Retrieval eCRF				X						
Sigmoidoscopic Evaluation of Anastomosis and anchoing site							X		X	
AEs	X	X	X	X	X	X	X	X	X	X§
Ostomy Reversal										X

*The Usability Questionnaire will be completed for first two Colovac subjects for the PI at each US site to assess any deployment challenges or technical difficulties that occur during Colovac implantation.
**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.

***Starting on Day 2, CRP will be tested every 2 days during hospitalization

† If device is removed before Day 10 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.

‡ If subject is converted to diverting ostomy, LARS QOL will only be collected at follow-up visits after ostomy reversal.

§ AEs related to the stoma creation or reversal procedure will be collected

Day 0 – Colovac placement: The device will be implanted according to the Instructions for Use. Record the length of the sheath from the stent to the anus, using the scale printed on the sheath; and use a suture knot to mark the position at 1 cm from the anal margin.

Any AEs that occur during the procedure will be recorded on the AE eCRF.

A baseline x-ray of device position will be obtained on Day 0 or Day 1.

If the subject is enrolled in the non-randomized run-in cohort, the Usability Questionnaire will be completed.

Hospitalization Period/Colovac Device Insertion Period: Day 1 – Day 10 (-1/+2 days)

Subjects will be hospitalized until the Colovac device is retrieved. To avoid stent obstruction, the patient should receive a low-residue diet (use of antidiarrheal medication such as Loperamide (Imodium) is not recommended). It is recommended that stool consistency be monitored to ensure that it remains soft but not liquid. Adjuvant therapy should not be initiated prior to retrieval of the Colovac device.

If not obtained on Day 0, a baseline x-ray documenting device position will be obtained on Day 1 and anytime that migration is suspected. Otherwise, additional x-rays documenting device position are optional.

Clinical and device monitoring will be performed, and findings will be recorded twice daily during hospitalization.

Patient Daily Monitoring includes:

Vital signs (Body temperature, Pulse, PE) and starting on Day 2, Serum CRP Levels every 2 days*

Device-related monitoring* will be performed twice daily according to the Instructions for Use and includes:

Visual vacuum indicator on the vacuum bottles, which raises up to indicate low level of vacuum in the bottles. Additionally, the Vacuum Loss Alert System provides continuous vacuum monitoring and visual and auditory alerts indicating a low level of vacuum in the bottles. The System is intended for use in conjunction with the visual vacuum indicator. If low level of vacuum is indicated by either monitoring method, the vacuum bottles should be replaced according to the SafeHeal Vacuum Loss Alert System IFU.
Presence of fluid in the high-volume vacuum bottles
Absence of blockage in the vacuum tubes
Mandatory change of the high-volume vacuum bottles at least every 24 hours. One bottle is changed in the morning and one in the afternoon to ensure that a vacuum is constantly maintained.

* See Treatment Algorithm Flowchart in Section 0 for additional information if findings are abnormal during the device implantation period.

Length of the sheath protruding from the anus. Using the suture on the sheath as a reference, check the sheath length protruding from the anus twice daily, and notify the surgeon if the sheath length has increased by more than 2 cm in 24 hours, or 3cm since the initial recording of sheath length. This is a potential sign of migration, in which case radiological imaging should be used to verify the device position. Day 2 only: The sheath may be trimmed using standard surgical scissors, so that the sheath protrudes by5 cm in length from the anal margin.

Day 9 only: EQ-5D-5L and LARs Score quality of life questionnaires will be completed by the subject

EQ-5D-5L Quality of Life (QOL): This questionnaire comprises the following five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression. Each dimension has five response levels: no problems, slight problems, moderate problems, severe problems, unable to/extreme problems. Additionally, the EQ VAS records the respondent's overall current health on a visual analogue scale where the endpoints are labelled "The best health you can imagine" and "The worst health you can imagine". The total score for the EQ-5D-5L ranges from 5-15, where a high score represents more severe or frequent problems. Low Anterior Resection Syndrome (LARS) Score QOL: This questionnaire consists of five items that include: frequent bowel movements, gas, and fecal incontinence, fragmentation, and urgency. The LARS score ranges from 0-42, where 0 is no symptoms and 42 is all symptoms at least once per week.

Any AEs that have occurred since the previous daily monitoring will be recorded on the AE eCRF.

Day 9 – CT Scan: A double (rectal and IV) contrast CT Scan with 1mm thick slices for acquisition and 2 mm thick slices for reconstruction will be performed at Day 9 (+3 days). Images will be recorded and analyzed to determine the presence or absence of leak and the description of the leak (if applicable). Information will be reported in the eCRF. Any AEs that occur during the procedure will be recorded on the AE eCRF.

Day 10 – Colovac Device Retrieval:

The following steps will be performed for all subjects at Day 10 (-1/+2 days) Note that these procedures may be performed: in the endoscopy unit if anastomosis is healed or in the operating room if the anastomosis is not healed completely, based on the findings of the CT scan performed on Day 9.

If the CT scan described above at Day 9 (+3 days) has not been performed prior to the day of retrieval, perform it before retrieving the Colovac Device.

The Colovac Device will be retrieved according to the Instructions for Use.

Note: An endoscopic examination will be performed *before* the device retrieval to confirm diversion of fecal stream from the anastomosis using the Boston Bowel Preparation Scale (BBPS) score (BBPS = 3). A still image of the circumference of the anastomosis should be obtained and provided to the Sponsor.

An endoscopic examination will be performed after the device retrieval to assess the mucosa appearance at the anchoring site of the Colovac Device. This examination will be video recorded and the mucosa condition above and at the Colovac anchoring site will be assessed by the clinician for bleeding, ulceration or perforation. A recording of the video should be provided to the Sponsor.

Assessment of the anastomosis status per the clinician's standard practice.

See Instructions for Use for additional post-retrieval guidance.

Any AEs that occur during the procedure will be recorded on the AE eCRF.

If the anastomosis has not healed completely, the following may also be performed:

Diverting Ostomy with patient management according to the standard of care.
Any AEs that occur during the procedure will be recorded on the AE eCRF.

Follow-up Visits

Study follow up visits are planned at the following intervals after the index surgery:
1 Month (+/- 14 days)
3 Months (+/- 14 days) – can be conducted over the phone*
6 Months (+/- 30 days)
9 Months (+/- 30 days) – can be conducted over the phone*
12 Months (+/- 45 days)

* The 3 and 9-month visits may be conducted over the phone if these visits are not part of the investigator's standard of care.

At each visit, the quality of life questionnaires will be completed by the subject and WBC and hemoglobin will be tested. If subject is converted to a diverting ostomy, the LARS quality of life questionnaire will be completed by the subject at each visit following ostomy reversal.

At the 6 and 12-month visits, a sigmoidoscopic evaluation of the anastomosis and the device anchoring site will be performed to assess the anastomosis and the device anchoring site. Any AEs that the subject has experienced since the previous visit or phone call will be recorded on the AE eCRF.

ANASTOMOSIS COMPLICATIONS DURING THE COLOVAC IMPLANTATION PERIOD

Any subject presenting with clinical signs or symptoms suggestive of anastomotic leakage during the implantation period of the Colovac Device, before the device is removed on Day 10, will be treated as per standard clinical practice.

Subjects with clinical signs or symptoms indicative of anastomotic leakage will undergo CT scanning. 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.

If reoperation is required and the decision is made to perform an ostomy with stoma creation, the Colovac Device will be removed.

Anastomotic Leakage may be symptomatic or asymptomatic.

Symptomatic anastomotic leakage includes one or more of the following clinical findings and patient symptoms, and is confirmed by radiographic study:

Abdominal pain

Fever (greater than 100.4 °F or 38°C)

Elevated CRP compared to the day before

Elevated WBC compared to the day before

Asymptomatic anastomotic leakage is defined as a lack of integrity of the anastomosis observed under the CT Scan examination (presence of air bubbles indicating the presence of a leak and/or evidence of rectal contrast leaking through the anastomosis) which may be due to incomplete healing, a fistula or dehiscence.

STUDY COMPLETION

When a subject completes the 12-month follow-up visit, the subject has completed the study and the End of Study Form should be completed. Patients who prematurely withdraw from the study prior to treatment do not require a 12-month visit and will continue to receive standard of care treatment.

WITHDRAWAL FROM THE STUDY

Study subjects can withdraw consent at any time, for any reason, specified or unspecified, and without penalty or loss of benefits.

Patients may also be withdrawn from the study for the following reasons:

Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that participation in the study is not in the best interest of the patient

Any other medical decision by the Investigator

Patient lost to follow-up

Patient who becomes prisoner or becomes hospitalized for treatment of either a psychiatric or physical (e.g., infectious disease) illness

Termination of the study by the sponsor

If a subject withdraws or is withdrawn from the study, the reason(s) for withdrawal (if offered) and the person withdrawing the patient, must be recorded on the End of Study Form. Regardless of the reason for withdrawal, data available for the subject at the time of withdrawal, including the reason for

withdrawal, will be collected on the Case Report Form. Subjects that withdraw from the study can continue to receive standard of care treatment as needed, outside of the study. Withdrawn subjects will not be replaced in the study.

If a subject is lost to follow-up, at least three attempts (including a certified letter) must be made by the investigator to contact the subject. These attempts will be documented in the subject's medical record.

ADDITIONAL SAFETY ASSESSMENT

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, safety or performance. Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling.
>
> All investigational device deficiencies will be documented in the eCRF. Devices that undergoes such deficiency will be returned to the device legal manufacturer (CMI) 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 CMI after appropriate decontamination per hospital guidelines.

Device deficiencies that did not lead to an adverse event but could have led to a serious adverse event

> a) if either suitable action had not been taken,
>
> b) if intervention had not been made, or
>
> c) if 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).[38]

All investigational device deficiencies will be documented on the eCRF. Devices that fail or malfunction will be returned to the device manufacturer (CMI) for analysis in the provided biohazard boxes with copies of the relevant eCRFs for failure and/or malfunction.

Returned Colovac devices will be examined in detail by the manufacturer.

MALFUNCTION

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.

USE ERROR

User action 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.

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.

ADVERSE EVENTS

All Adverse Events will be recorded on the AE eCRF.

DEFINITIONS

Adverse Events (AE) per ISO14155:2020

The definition of an adverse event is:

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, 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 and other persons the definition is restricted to events related to investigational medical devices.

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:

death,
serious deterioration in the health of the subject user or other persons that either resulted in:
1) a life-threatening illness or injury,

2) a permanent impairment of a body structure or a body function,

3) hospitalization or prolongation of patient hospitalization,

4) medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
5) chronic disease
fetal distress, fetal death or a congenital physical or mental impairment or birth defect

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

Serious Adverse Device Effect (SADE)

The definition of a Serious Adverse Device Effect is:

An SAE for which relationship to device has been established as possible, probable or definite.

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.

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.

POTENTIAL ADVERSE EVENTS

Potential adverse events include the following:
The general complications of any colorectal surgery.

Pelvic complications
- Anastomotic bleeding
- Anastomotic stricture
- Anastomotic fistula
- Anastomotic leakage
- Anastomosis dehiscence
- Pelvic abscess, collection
- Colonic ischemia
- Peritonitis

Ileus
Small bowel obstruction
Incisional hernia

Bleeding

Organ injury (e.g. bladder, bowel, ureter)

Nerve tissue injury

Surgical Site Infection

Prolapse

Acute renal failure

Sepsis

AEs associated with potential stoma placement/stoma reversal

Adverse events that may probably be caused by or associated with the use of the Colovac Device (during and after implant period) include:

Complications from device malfunction that lead to early removal of device and stoma conversion (e.g.

stent collapse) such as:

Pelvic complications (abscess, collection)

Anastomosis complications (leakage, fistula, dehiscence)

Peritonitis

Sepsis

Colon perforation, obturation or occlusion

AEs associated with stoma conversion procedure

Ileus

Small bowel obstruction

Colonic ischemia

Colonic stenosis

Colon wall damage (e.g. inflammation, hyperplasia, fibrosis, edema, erosion, ulceration)

Abdominal/Anal pain

Temporary feces and gas incontinence

Diarrhea or constipation

Inflammation of skin around the anus

Prolapse

Complication associated with an attempt to reposition the Colovac Device (although Warnings instruct not to re position the Colovac Device)

Complication associated with having to remove the Colovac Device surgically – if endoscopic retrieval is impossible

Adjacent organ injury due to a broken stent wire poking through the colon

Additional complications reported for other colorectal stents:

Tenesmus

Fecal impaction

Bacteremia/fevers

Foreign body sensation

Intestinal colic (pain not related to operative site)

Bleeding/blood from anus

Nausea

Inability to eat

Cramping

Adverse events (biological responses) potentially associated with the SafeHeal Vacuum Loss Alert System:

a) Erythema
b) Edema
c) Irritation
d) Delayed Type IV hypersensitivity
e) Allergy
f) Immune response

Other reactions

Adverse events associated with the stoma:

a) Skin complications

Peristomal dermatitis

Skin irritation

Skin breakdown

b) Parastomal ulceration
c) Parastomal hernia
d) Stoma complications:

Stoma necrosis

Stoma retraction

Stoma prolapse

Stoma stenosis

e) Dehydration
f) Intestinal Obstruction
g) Infection
h) Sepsis

Adverse events associated with stoma reversal:

Leakage (at the stoma closure site)

Surgical Site Infection

Hernia at stoma site

Small bowel obstruction

Ileus (no return of bowel function in 7 days per NSQIP definition)

Renal failure

Infection

Sepsis

Complications that prevent stoma-closure by 12 Months

Medication side effects, especially anesthesia reactions, including:

Respiratory insufficiencies

Sedation-induced apnea

Pneumonia

Hypotension

Cardiac arrest (death)

Nausea and/or vomiting

AE REPORTING

All the adverse events identified by the physician or the patient during the study must be reported on the AE eCRF, regardless of classification, seriousness, intensity, outcome or 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 device (including implantation and removal procedures), VLAS 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 investigational device, the VLAS, the LAR surgery and the stoma.

Not related	Relationship to the device or procedures can be excluded when: • 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; 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.
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	The serious adverse event is associated with the investigational device, or with procedures beyond reasonable doubt when: • 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 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:

a. Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
b. Moderate: minimal, local or noninvasive intervention indicated; limiting
c. 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

In addition, the severity of the event will be assessed using the Clavien-Dindo classification[32,33] shown in Table 7.

Table 7: 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, subarrachnoidal 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 in Section 0.
- Action taken
- Date of resolution
- Outcome

All adverse events will be followed until the event is resolved or stabilized and/or deemed permanent. An independent Clinical Evaluation Committee (CEC) will be responsible for adjudicating the severity, seriousness and relatedness of the adverse events. 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 Section 0.

A Data Safety Monitoring Board (DSMB) will monitor the safety of the investigational device, the progress of the clinical investigation and the critical performance endpoints. The DSMB responsibilities are discussed in Section 0.

If the AE meets the criteria for an SAE, the investigator must send the completed AE form by email or fax to the sponsor within 3 days.

In all cases, the sponsor notifies the FDA, National Competent Authorities (NCAs), Notified Bodies (NBs) and the Institutional Review Boards(IRBs)/Ethics Committees (ECs) of the SAE, if required. For all SAEs, the sponsor classifies the event as expected/unexpected using the list of anticipated adverse events provided in the labeling.

The sponsor will send an updated MDCG 2020-10/2 “Clinical Investigation Summary Safety Report Form” to the National Competent Authorities (NCAs) of the EU member states each time a new reportable event or a new finding to an already reported event is to be reported as per the MDR 2017/745 reporting requirements.

CLINICAL EVALUATION COMMITTEE

An independent CEC will conduct a medical review of all AEs at regular intervals and an urgent review of select SAEs described in Section 0. 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 adjudicate, at a minimum, all AEs and subsequent surgical interventions. The CEC will operate under a charter that documents the process for adjudication of data for this study.

The CEC is responsible for reviewing data extracted from the clinical database, reviewing applicable definitions, and determining final classifications for adjudication parameters. For AEs, classification includes severity, seriousness, relatedness to the index surgery, the Colovac device (including implantation and removal procedures) and the stoma (including creation and reversal procedures), The CEC will review all adverse events to determine the severity, seriousness, and relatedness to the index surgery, the Colovac device (including implantation and removal procedures), the VLAS ,and the stoma (including creation and reversal procedures),

The CEC will be blinded to the study treatment (to the extent possible) and will assess the adverse events according to the CEC Charter and this protocol. SafeHeal and contract research organization personnel may facilitate and participate in a CEC meeting but will be non-voting members.

URGENT REVIEW OF SELECT SAES

The following SAEs will undergo urgent review by the CEC to determine the causality of the event:

Clinically significant and symptomatic leaks (as defined in Section 6.3.5 of the protocol) requiring emergent surgical intervention

Leak related sepsis that meets all of the following criteria and is ISREC Grade C (as described in Section 6.3.5 of the protocol):

- Abdominal pain
- Fever (greater than 100.4 °F or 38°C)
- Elevated CRP compared to the day before
- Elevated WBC compared to the day before

(Leak must be confirmed via radiographic or endoscopic evaluation)

Note: This definition is consistent with Section 6.5.4 of the protocol.

Mechanical injury to the bowel and/or anastomosis requiring emergent surgical intervention

Death

These SAEs will be evaluated by the full CEC within 72 hours of the Sponsor's awareness of the event. The SAE form will be provided to the CEC. In its urgent meeting, the CEC will determine the causality of the event, and if the number or rate of device related events triggers one of the study stopping criteria, implantation of the device will be stopped until further evaluation by the DSMB during an ad hoc meeting.

The study stopping criteria and triggers are listed below in Table 8. Note that some of the criteria consider probably and definitely/causally related events, some consider only possibly related events and some consider possibly, probably and definitely related events.

Table 8: Stopping Criteria and Triggers

Study Stopping Criteria	Stopping Criteria Triggers	
	Occurrence of Device Related Event	Device Relatedness
Clinically significant and symptomatic leaks (defined in Section 6.3.5 of the protocol) requiring emergent surgical intervention		
Leak related sepsis that meets all of the following criteria and is ISREC Grade C Abdominal pain Fever (greater than 100.4 °F or 38°C) Elevated CRP compared to the day before Elevated WBC compared to the day before (Leak must be confirmed via radiographic or endoscopic evaluation)	2 events >10%	Probably or Definitely Possibly
Mechanical injury to the bowel and/or anastomosis requiring emergent surgical intervention		
Death	1 event	Possibly, Probably, Definitely

Note that regardless of CEC determination on causality of the event, all events that triggered the stopping rules will be reported to FDA within the required timeframe for reporting.

REGULAR REVIEW OF ALL AES

During the regularly scheduled meetings, the CEC will assess all AEs, and determine final classifications for adjudication parameters, including: severity, seriousness, relatedness to the index surgery, the Colovac device (including implantation and removal procedures), the VLAS and the stoma (including creation and reversal procedures), The CEC will review all adverse events to determine the following:

The relationship of the AE to the index surgery, the Colovac device (including implantation and retrieval procedures), VLAS and the ostomy with stoma creation and reversal procedures;

The seriousness of the adverse event; and

The severity of the adverse event.

Additionally, the CEC will review the video recorded during the post-retrieval endoscopy to adjudicate the mucosal appearances.

DATA SAFETY MONITORING BOARD

An independent DSMB will assess the progress of the clinical investigation, the safety data and the critical performance endpoints, and recommend to the sponsor whether to continue, suspend, modify,

or terminate the clinical investigation. The DSMB will consist of a minimum of three (3) non-SafeHeal employed physicians that are not participating investigators for the study, including a DSMB chairperson. Other than receiving compensation from the sponsor for their time spent as DSMB members, DSMB members should have no other relationship with the CRO, sponsor or investigator that could impair the members' ability to objectively review study data.

An ad hoc meeting will be called to review the study safety if the CEC causality determinations of the criteria listed in Section 0 trigger any of the study stopping criteria listed above in **Table 8**.

The DSMB shall follow a formal Charter which incorporates stopping rules.

SUSPENSION OR PREMATURE TERMINATION

If the stopping rule included in the DSMB charter is met, the DSMB may recommend suspending or terminating the study. Additionally, if the Sponsor and/or the DSMB determine that the study presents an unacceptable risk, the study may be terminated. Termination shall occur not later than 5 working days after the sponsor and/or the DSMB make this determination. SafeHeal will notify all participating investigators, IRBs/Ethics Committees, FDA and other appropriate regulatory authorities of the termination of the investigation.

STATISTICAL ANALYSIS PLAN

CO-PRIMARY STUDY ENDPOINTS.

This study is intended to demonstrate the safety and effectiveness of the Colovac device using two co-primary endpoints. A closed testing method in which each of the primary endpoints specified below are compared using the full alpha will be used. Study success requires that the Colovac group successfully reject the null hypothesis for both of the individual primary endpoints. Because non-inferiority must be successfully shown for both endpoints for study success, the type I error rate is preserved at 5% for the entire primary endpoint.

As mentioned above, the primary study endpoint will consist of two individual co-primary endpoints, one safety and one efficacy measure. Specifically, the following endpoints are included as individual co-primary endpoints:

The primary safety endpoint is the rate of subjects with post-operative major complications within 12 months.

The primary effectiveness endpoint for the Colovac-treated patients is: A clinically meaningful reduction in stoma creation rate

PRIMARY SAFETY ANALYSIS

The primary safety hypothesis is that the proportion of subjects with post-operative major complications within 12 months in the Investigational group is non-inferior to the proportion in the Control group using a 10% margin of non-inferiority. The hypotheses are as follows:

Definitions:

p_I : Proportion of subjects with postop major complications in the Investigational group.

p_C : Proportion of subjects with postop major complications in the Control group.

For the specified constant, $0 < \delta < 1$, the hypotheses of non-inferiority are:

$H_0: p_I - p_C > \delta$ vs. $H_A: p_I - p_C \leq \delta$.

The test will be based on the upper bound of a one-sided 95% confidence interval for the difference in proportions, Investigational minus Control. A conclusion of non-inferiority is supported if the upper bound of the confidence interval is <0.10.

Non-inferiority Margin

This margin of δ=0.10 is an appropriate value for the non-inferiority margin because the expected major complication rate in this study is approximately 40% for the Colovac group, and 48% for the Control group. As these rates have nearly the highest variance in the binomial distribution, use of a 10% margin is a reasonable choice per Chow and Song[39]. This article mentions a “classical method” of determining the non-inferiority margin. As an example of a NI margin for a binary response (e.g. a success or failure rate), this method indicates that as a general rule, if the success rate is between 50% and 80% (failure rate between 20% and 50%), then a non-inferiority margin or equivalence limit of up to 20% could be chosen for non-inferiority trials. Although the expected major complication rate is approximately 40%, 10% was selected as a more conservative margin.

PRIMARY EFFICACY ANALYSIS

Study success will be defined as a clinically meaningful stoma reduction rate in the Colovac patients AND statistical non-inferiority on the primary safety endpoint (Colovac vs. Control). A benefit-risk assessment of all the clinical data will be performed to determine the ostomy reduction rate that balances the risk that device use may pose. This ostomy reduction rate will be considered clinically meaningful and provide the basis for the actual performance goal for this endpoint.

For study planning and sample size calculation purposes, the clinically meaningful reduction in stoma creation is assumed to be 50%, which would require that more than half of all patients in the IDE Colovac group avoid a stoma creation Note that ostomy avoidance is expected in approximately 70% of Colovac

patients and that, regardless of the final study results, the ostomy avoidance percent in the Colovac study group is expected to exceed 50% (lower limit of the 95% confidence interval of the point estimate).

However, a benefit-risk assessment of all the clinical data will be performed to determine the ostomy reduction rate that balances the risk that device use may pose. This ostomy reduction rate will be considered clinically meaningful and provide the basis for a performance goal this endpoint.

Clinically Meaningful Reduction

The following factors will be considered in a Benefit-Risk assessment related to the ostomy avoidance rate.

The standard of care relies on the ostomy procedure to allow for anastomosis protection and decrease the need of a permanent stoma. Thus, by definition, the standard of care treatment would result in a stoma creation rate of 100%. As a result, a relatively small reduction in stoma creation is likely clinically meaningful. Additionally, we expect that the per-protocol use of Colovac will not result in a higher risk to subjects than the standard of care. However, as the clinical safety for Colovac has not yet been established, the potential risks and benefits of the Colovac and Control treatments are assessed.

The potential risks associated only with the use of the Colovac device in the IDE study are the risks related to a longer hospital stay, harm due to a failure of the device, risks from a later, more complicated ostomy surgery due to failure of the device, and the risks of late (> 10 days) AL and need for subsequent treatment. The potential risks associated with the standard of care, and potentially avoided by the use of Colovac, are the risks of ostomy, the stoma-related risks, the risks of stoma reversal and the risk of a significantly higher proportion of permanent stomas.

The potential benefit associated only with the Colovac device is avoidance of ostomy which patients highly value. Having a stoma can potentially decrease an individual's quality of life and therefore their emotional state must be regularly assessed throughout this time. Not only do patients with stomas have to cope with loss of control over their elimination of feces, but may also experience negative changes to body image and sexual function, social isolation, stigma, embarrassment and decreased mood.[1]

Up to a fourth of patients will experience negative psychological symptoms immediately following a stoma creation, most commonly anxiety and depression, and more rarely, suicidal ideation. About the same percentage of patients were still experiencing negative psychological symptoms a year following their stoma creation.[2,3]

COMPOSITE SECONDARY EFFECTIVENESS ENDPOINT

As the composite secondary effectiveness endpoint cannot be assessed in the control group, the control group cannot be used as comparator to determine success. Thus, a performance goal (PG) will be established for this endpoint. The performance goal will be further defined in a separate Statistical Analysis Plan.

USABILITY ANALYSIS

Two non-randomized Colovac subjects for the PI at each US site will be included in a run-in component of the study. Note that European sites with no experience implanting the Colovac device will enroll 2 subjects per site in a European run-in component.

In addition to the other eCRFs, the Usability Questionnaire eCRF will be completed for each run-in patient to assess any implantation challenges or technical difficulties, as well as to capture any adverse events that occur during Colovac implantation. Lastly,it is highly recommended that the run-in Colovac implantations are video recorded (the laparoscopic view would be recorded). Other than completion of the Usability eCRF, the run-in subjects will undergo the same treatment, examinations, and procedures as the Colovac subjects in the randomized component. However, subjects in the non-randomized run-in component will be analyzed separately from the subjects in the randomized component. Upon completion of the device implantation procedure on the first 10 run-in subjects, the data will be summarized and reported to FDA.

DETERMINATION OF SAMPLE SIZE

In order to calculate the sample size for the randomized component of the study, the sample size needed to obtain 90% power for each of the co-primary endpoints was calculated. The endpoint requiring the largest sample size to maintain 90% power was the primary safety endpoint. Therefore, this is the sample size used in this study to ensure that we have a sufficient number of patients to test each of the primary endpoints with at least 90% power.

Regarding the Primary Safety Endpoint:

The primary safety hypothesis to be tested is that the proportion of *Colovac* subjects with a major post-operative complication is non-inferior to the proportion in the Control group.

The incidence of post-operative complications following colorectal surgery with stoma creation has been extensively described in the literature. Based on published rates of postoperative complications following low anterior resection with a diverting ileostomy, the overall incidence rate of complications ranges from 33% to 52% (see Appendix 3 for the meta-analysis plan and report). Additionally, an estimate of the rate of major complications in the Control group was calculated using data collected in a retrospective cohort study (SH-001). The major complication rate for this retrospective cohort is shown in Table 9 below. Thus, an estimated major complication rate of 48% seems reasonable for the Control group. A summary of the SH-001 Study is provided in Appendix 4.

Table 9: Major Complications for SH-001 Study

n/N (%)	Exact 95% CI
73/153 (47.71%)	(39.6, 55.9)

Regarding the treatment arm, preliminary results obtained in the SAFE-1 trial demonstrated an overall 33% major complication rate used in this study during the 3 month study follow-up. Additionally, the major complication rate estimated for Control group (discussed above) was adjusted to provide another estimate for the major complication rate for the Colovac group. For example, the rate of stoma related AEs in the control arm was reduced adjust for the lower rate of stoma creation expected in the Colovac group, while the rate of LAR-related complications was assumed to be the same in both groups. The estimated rate was calculated using the high end and low end of the range of the assumptions, which resulted in an expected complication rate for the Colovac group of 31 – 44%. Thus, a major complication rate of 40% seems reasonable for the Colovac group.

Assuming a 40% vs 48% estimated rate of major complications in the Colovac treatment vs the standard of care arm, and a non-inferiority margin of absolute 10%, iterative simulation of the proposed adaptive design was performed to determine the maximum sample size and associated operating characteristics. This simulation showed that a maximum sample size of 342 randomized patients would produce 90% power under the expected device and control rates, assuming a 7% rate of loss to follow-up.

Regarding the Primary Efficacy Endpoint:

Study success will be defined as a clinically meaningful stoma reduction rate in the Colovac patients AND statistical non-inferiority on the primary safety endpoint (Colovac vs. Control). The clinically meaningful reduction in stoma creation is assumed to be 50%, which would require that more than half of all patients in the IDE Colovac group avoid an ostomy. Note that ostomy avoidance is expected in approximately 70% of Colovac patients and that, regardless of the final study results, the ostomy avoidance percent in the Colovac study group is expected to exceed 50% (lower limit of the 95% confidence interval of the point estimate). However, a benefit-risk assessment of all the clinical data will be performed to determine the ostomy reduction rate that balances the risk that device use may pose. This ostomy reduction rate will be considered clinically meaningful and provide the basis for the actual performance goal for this endpoint.

Assuming a success rate of 70% for the Colovac treatment, a total of 70 evaluable patients has 90% power to reject H_0 at a 2-sided $p<0.05$ significance level.

Total Sample Size:

Based on the primary endpoints, the larger sample size of 342 subjects was selected for the randomized component of the study. At least 50% of the randomized subjects will be enrolled at US sites.

The non-randomized run-in component will enroll up to 30 Colovac subjects (2 per site at up to 15 US sites) for a total of up to 372 subjects enrolled.

POPULATIONS FOR ANALYSIS

SAFETY POPULATION

The Safety Population will include all subjects randomized in the study who receive the study treatment, i.e. Colovac or Standard of Care. Subjects will be analyzed according to the treatment actually received. If a subject received Colovac for any duration, the subject will be analyzed in the Colovac treatment group. Otherwise the subject will be included in the Standard of Care group. The Safety Population will be used for all safety-related analyses. This population will be used in the primary safety analysis and missing primary outcome data will not be imputed. All subjects who have the device removed before Day 10 due to a device-related reason will be included in the assessment as failures.

INTENTION TO TREAT POPULATION

All randomized subjects comprise the ITT population and will be tracked. Subjects will be analyzed according to the randomized treatment assignment. This population will be used in the primary efficacy analysis. All subjects who have the device removed and require conversion to ostomy will be included in the assessment as failures. Any missing primary outcome data will be imputed using multiple imputation techniques.

The ITT population will also be used in all other efficacy analyses, without imputation for missing data.

PER PROTOCOL POPULATION

The per-protocol dataset is a subset of subjects who are included in the ITT dataset. Subjects who have major study deviations (i.e., those who do not meet the inclusion/exclusion criteria, those who receive a treatment other than one of the study treatments, or those having other study deviations that could potentially affect clinical outcomes) will be excluded from this dataset. The CEC will determine which study deviations are major.

The per-protocol population will only be used for the analysis of the primary endpoints as a sensitivity analysis.

STATISTICAL METHOD AND ANALYSIS

For general data summary, the number of subjects with data, mean, standard deviation, median, minimum and maximum will be presented for continuous data. Frequency and percentage will be presented for categorical data.

SECONDARY EFFECTIVENESS ANALYSIS

To limit the overall type I error rate to 2-sided 0.05 for the secondary effectiveness endpoints, a gated hierarchical testing approach will be adopted. Four of the secondary effectiveness endpoints will be tested in the order presented below, and as follows:

Cumulative hospital stay post-discharge

Comprehensive Classification Index (CCI)

LARS quality of life

EQ-5D-5L quality of life

Testing will continue only if all previously tested null hypotheses of no difference have been rejected at the 2-sided alpha=0.05 significance level in favor of the Colovac treatment.

Hypotheses and associated tests for the secondary effectiveness endpoints are shown in Table 10.

Table 10: Planned Sequence of Key Secondary Effectiveness Tests

Target Claim	Statistical Hypotheses	Statistical Test
The mean cumulative length of hospital stay is significantly less for Colovac subjects through 12 months than the mean cumulative length of hospital stay for Control subjects through 12 months.	$H_0: \pi_I = \pi_C$ $H_a: \pi_I < \pi_C$ Where, π_I = The mean cumulative length of hospital stay for Colovac subjects through 12 months π_C = mean cumulative length of hospital stay for Control subjects through 12 months	T-test
The mean CCI for Colovac subjects through 12 months is significantly less than the mean CCI for Control subjects through 12 months.	$H_0: \pi_I = \pi_C$ $H_a: \pi_I < \pi_C$ Where, π_I = The CCI for Colovac subjects through 12 months	T-test

Target Claim	Statistical Hypotheses	Statistical Test
	π_C = The CCI for Control subjects through 12 months	
The mean LARS QOL for Colovac subjects at 6 months is significantly higher than the mean LARS QOL for Control subjects at 6 months.	$H_0: \pi_I = \pi_C$ $H_a: \pi_I > \pi_C$ Where, π_I = The mean LARS QOL for Colovac subjects at 6 months π_C = The mean LARS QOL for Control subjects at 6 months	T-test
The mean ED-5Q-5L QOL for Colovac subjects at 1 month is significantly higher than the mean ED-5Q-5L QOL for Control subjects at 1 month.	$H_0: \pi_I = \pi_C$ $H_a: \pi_I > \pi_C$ Where, π_I = The mean ED-5Q-5L QOL for Colovac subjects at 1 month π_C = The mean ED-5Q-5L QOL for Control subjects at 1 month	T-test

SECONDARY EFFECTIVENESS ENDPOINTS

Secondary Effectiveness Endpoints Comparing the Colovac and Standard of Care Arms

Cumulative Length of Hospital Stay through 12 Months post-discharge: Total length of hospital stay (in days) through the 12-month visit will be compared between the two study arms. As skewed data distributions are expected, an appropriate non-parametric method such as the Wilcoxon's rank sum test or the logrank test (should there be censored data) will be used for analysis.

Comprehensive Classification Index (CCI): The CCI is the sum of all AEs, weighted by their severity. The CCI will be collected and compared between the treatment group and the control group. The CCI includes all postoperative complications and thus, is more comprehensive and more sensitive than other safety endpoints. The CCI is calculated on the basis of tabulated complications classified according to

the Clavien-Dindo classification. The CCI will be summarized and compared between the two arms as continuous measures.

LARS Quality of Life: The Low Anterior Resection Syndrome (LARS) QOL at 6 months post-index surgery will be compared between study arms using the LARS questionnaire. The questionnaire consists of five items that include: frequent bowel movements, gas, and fecal incontinence, fragmentation, and urgency. The LARS score ranges from 0-42, where 0 is no symptoms and 42 is all symptoms at least once per week. The LARS score at 6 months post-index surgery will be compared between the two treatment arms as a continuous measure. Note that as the LARS questionnaire cannot be completed by subjects in the Control arm until after ostomy reversal, if a Control subject does not have a score at 6 months, the score at the next closest time point will be used. The mean, median, minimum and maximum will be descriptively presented for each arm.

EQ-5D-5L Quality of Life (QOL): Patient QOL at 1 month post-index surgery will be compared between study arms using EQ-5D-5L questionnaire. The EQ-5D-5L comprises the following five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression. Each dimension has five response levels: no problems, slight problems, moderate problems, severe problems, unable to/extreme problems. Additionally, the EQ Visual Analogue Scale VAS records the respondent's overall current health on a visual analogue scale where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The 5-15 total score for the EQ-5D-5L descriptive dimensions will be summarized as ordinal data for the two treatment arms and compared by Cochran-Mantel-Haenszel test for ordinal data. The VAS score will be summarized and compared between the two arms as continuous measures.

Sigmoidoscopic assessment of anastomosis: The anastomosis will be assessed at 6 and 12-months post-surgery.

Secondary Effectiveness Endpoints for Colovac Arm Only

As defined in Section 0, the following secondary endpoints pertain to the Colovac device arm only. These will be summarized according to Section 8.4. Additionally, 95% confidence intervals for the estimates will be included. For endpoints (or sub-items of an endpoint) with a binary Yes or No outcome, the proportion of subjects with a Yes answer will be presented with a 95% confidence interval. For endpoints with a categorical outcome, e.g. surgeon's rating of 1 – 5 score, or mucosal appearance of bleeding or ulcerated or perforated, the percentage of subjects in each category will be presented.

Assessment of the composite effectiveness endpoint at Day 10: The composite effectiveness endpoint is defined as

Diversion of fecal contents from the anastomosis site confirmed by endoscopic evaluation for the absence of feces between the sheath and the colonic wall AND the absence of clinically significant and symptomatic AL; AND
Absence of clinically significant migration

Assessment of fecal diversion at anastomosis site before device retrieval: Fecal diversion will be confirmed by an endoscopic examination using the BBPS score (BBPS = 3)
Assessment of clinically significant and symptomatic AL: Clinically significant and symptomatic AL is defined as AL with ISREC classification of severe Grade B and Grade C.

Assessment of Clinically significant migration: Clinically significant migration is evidenced by migration of entire stent 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 or expulsion of the device.

Elective Ostomy Conversion Rate through 12 Months: The rate of elective ostomy creation through the 12-month visit

Assessment of mucosal appearance and anastomosis integrity after device retrieval:

Mucosal appearance at anchoring site classified as Bleeding, Ulcerated, Perforated.
Assessment anastomotic integrity will be performed as per surgeon discretion / hospital standard of care. Anastomosis will be classified as Normal, Presence of Leakage, Presence of Dehiscence.

Patient acceptance and tolerability, including

Usage of external sheath and external vacuum tubes through the anus rated on a scale from 1 full acceptance to 5 no acceptance)
Presence of vacuum system (rated on a scale from 1 full acceptance to 5 no acceptance)

Assessment of mucosal appearance at anchoring site at 6 and 12 months after surgery

Mucosal appearance at anchoring site classified as Bleeding, Ulcerated, Perforated.

EXPLORATORY ENDPOINTS

Overall Morbidity: All reported adverse events (AEs) will be collected and compared between the treatment group and the control group.

Assessment of anastomosis integrity on Day 9: Note that this assessment will occur prior to device retrieval for subjects in the Colovac Arm.

A double contrast CT Scan with a slice thickness of 1 mm in acquisition and 2 mm in reconstruction will be performed to check for anastomotic integrity. Anastomosis will be classified as Normal, Presence of Leakage, Presence of Dehiscence.

Subgroup analyses:

The primary endpoint and secondary endpoints will also be analyzed separately according to the following subgroups:
Neoadjuvant chemoradiation. Subgroups will be Yes and No.
Type 2 Diabetes Mellitus. Subgroups will be Yes and No.
Age. Subgroups will be < 65 years and ≥ 65 years
Gender. Subgroups will be Male and Female.
BMI. Subgroups will be < 30 and ≥ 30
Colon diameter. Subgroups will be < 25, 25– 35, and > 35 mm.
Surgical approach: Subgroups will be open, laparoscopic, and robotic-assisted laparoscopic colorectal surgery
Anastomosis location: Subgroups will be coloanal and colorectal

These will be considered as exploratory without adjustment for multiplicity.

SAFETY ANALYSIS

The number and proportion of subjects with each individual major complication will be compared between Colovac vs. Standard of Care treatment, with a descriptive p value by Fisher's exact test. In addition, the frequency and percentage of subjects reporting 0, 1, 2, etc. major complications will be similarly analyzed.

A key safety endpoint is the rate of all morbidity, i.e. all reported adverse events. The number and proportion of subjects with each AE will be summarized by Colovac vs Standard of care with a descriptive p value by Fisher's exact test. Separate tables will be presented for (a) all reported AEs, (b) serious AEs (SAEs), (c) AEs leading to treatment discontinuation, (d) AEs leading to death, (e) relationship to device (f) relationship to ostomy, (g) relationship to LAR. A detailed listing of major complications will be provided to accompany the primary safety analysis result.

MISSING DATA

For the study's primary safety endpoint, substantial missing data are not expected for this severe disease condition. However, any missing data will be handled in the analysis as follows:

Data will be considered "missing" for the primary safety and efficacy endpoints if the endpoint cannot be calculated or is not available for a subject in the Intent-to-Treat population. Missing data will be accounted for in the primary safety and efficacy analyses as described in Sections 0 and 0. Note that all subjects who have the device removed and require conversion to an ostomy will be included in the assessment as failures.

The Safety and ITT population will be used in the primary safety and efficacy analyses, respectively.

In addition, sensitivity analyses will examine the sensitivity of the results to missing values of the primary efficacy outcome using the following analyses:

Tipping Point Analysis: Missing observations are replaced with values until the p-value for the primary hypothesis test is < 0.049 (if study result is ≥ 0.049) or ≥ 0.049 (if study result is < 0.049). Graph will show which imputations of success/failure for the missing values in the *Colovac* and control groups lead to a rejection of H_0, and which lead to a non-rejection of H_0.

Multiple Imputation Analysis: the primary efficacy analysis will be performed on the Safety population as a sensitivity analysis. Missing data will be imputed using multiple imputation. Multiple imputation covariates will include age, gender, BMI, neoadjuvant chemoradiotherapy, Type 2 Diabetes Mellitus, colon diameter, surgical approach and anastomosis location.

Per Protocol Analysis: the primary efficacy analysis will be performed on the PP population as a sensitivity analysis, without imputation for missing data.

RANDOMIZATION DETAILS

The randomization for this study is a 1:1 randomization scheme. The randomization table for the entire study cohort will be completed prior to start of the clinical trial. The randomization plan will be produced using SAS v 9.4 or similar software. Balanced randomization with block sizes (1:1, Colovac Group: Control Group) will be implemented. In the event that, post-randomization, no study treatment was given, randomization will not be reassigned; however, this case will not count toward the overall sample size. Randomization will continue with the next case enrolled until the minimum sample size is reached in both treatment groups. Randomization will be stratified by site, and each site will receive separate randomization plans using predetermined block sizes that will remain undisclosed to the sites.

ASSESSMENT OF POOLABILITY

The following analyses of poolability of the data will be performed:

The primary safety and efficacy analyses will be performed on the pooled (US+OUS) population of subjects. Each analysis will also be presented for the following subgroups:

Country and/or region
Gender
Clinical study site

The homogeneity of treatment effect by region (US/OUS) will be evaluated as follows for the primary efficacy and safety endpoints:

Primary safety endpoint: the uniformity of the treatment effect on the odds of a major post-operative complication for US and OUS subjects will be examined using the Breslow-Day test for homogeneity of odds ratios. The test will use a significance level of 0.15.

Primary efficacy endpoint: the uniformity of primary efficacy success for US and OUS subjects will be examined using a Fisher's Exact test to see if there is a significant difference in the proportions of subjects with successful outcomes for US and OUS subjects. This test will use a significance level of 0.15.

If there is no evidence of a significant difference in regions ($p \geq 0.15$), data from OUS and US will be pooled. However, the existence of a difference as demonstrated by the p-value alone does not necessarily invalidate the analysis in pooling data across regions. Thus, if $p < 0.15$ then the observed proportions for each US and OUS site will be examined qualitatively to assess site and region dependency as well as whether there are other reasons for the differences. Further, factors potentially contributing to this interaction will be examined, and a stratified analysis will be conducted, and results compared to overall study results to assess consistency.

INTERIM ANALYSIS SPECIFICATION

An interim analysis is planned to formally assess the sample size calculation for the primary safety endpoint of this study. A designated unblinded statistician, independent from the study, will conduct the interim analysis when approximately 50% (140 patients) have reached the 12 month time point. The observed effect size (proportion of subjects in each group with a major postoperative complication) at this interim time point will be estimated for analysis, spending 0.001 of the overall alpha-level of 0.05. This leaves 0.049 alpha for the final analysis. This is appropriate, as the study Sponsor is not expecting statistical significance, nor planning to stop the study, only to re-assess the sample size calculation. Furthermore, the effect of sample size adjustment through interim analysis has been shown to have negligible effect on Type I error rates[49]. The observed proportions at the interim time point will be used by the independent, unblinded statistician to re-calculate the sample size for the study. The effect size will not be shared with the Sponsor or with FDA, only whether or not an increase in the sample size is warranted. The independent, unblinded statistician will only report to the Sponsor the sample size required for 80% and 90% power given the data to that point. If the initial sample size is large enough to provide a minimum of 80% power (i.e. $n \geq n^*$), no action will be taken, and the trial will continue until all the planned number of subjects (n) are recruited. Otherwise, if $n < n^*$, an increase in sample size may be requested so that and the trial may continue until enough patients (n^*) have been recruited that the desired power is achieved. The final new sample size for is :

$$\boldsymbol{n_{new} = Max(n, n*)}$$

Therefore, if an increase in sample size is warranted by the re-calculation of the sample size requirements at the interim time point, it will only be reported how many more subjects are required in order to meet the study endpoint at sufficient power. The sample size will not be reduced as a result of the sample size re-calculation. The sample size will only be increased, if the reassessment is so indicated and permission from FDA has been obtained. If the reassessment does not indicate an increase in sample size, then the study will continue as originally planned.

DATA HANDLING

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).

IDE regulations (21 CFR 812) and GCPs require that the Investigator 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 10.4, Monitoring Procedures.

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 have been pseudonymized to comply with the applicable data security and protection rules (General Data Protection Regulation -GDPR). The Sponsor takes all necessary measures to prevent unauthorized access to their computers and that no data is lost. Only study personal directly involved in the conduct of the trial will have authorization to enter or access data in the clinical trial data base. 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.

The subject will receive all information as required by the EUGDPR, namely the identity and contact details of the controller, processor and Data Protection Officer (DPO),if applicable or data protection contact, the clinical research purposes, the legal basis for the processing, the recipients of the personal data, the transfer of the personal data to third countries and respective safeguards, the retention periods, the fair processing of his data, and all his/her data subject's rights. All details will be listed in the informed consent form.

Subject confidentiality and privacy is 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 IRB/IEC, regulatory agencies may inspect all documents and records required to be maintained by the 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 IRB/IEC, Institutional policies, or sponsor requirements.

Trial subject research data, which is for 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.

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.

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 IRB/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 ensure that all required documents are filed. The file will be inspected during monitoring visits.

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.

REGULATORY

SPONSOR RESPONSIBILITIES

SafeHeal, is the Sponsor of the clinical trial but study management activities will be conducted by a CRO. CMI is the manufacturer of the study devices. The Sponsor's responsibilities in the study include:
Provide study devices to participating study sites, in quantities sufficient to support study activities.
Provide all necessary training to investigators and study sites staff for using the investigational device properly and for executing the study.
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, mainly including coverage of costs specifically induced by the performance of the study.
Subscribe to an insurance policy covering specifically the potential risks directly related to the participation of the patients to the use of the investigational device in the scope of this clinical trial.
Establish all regulatory standards per national and local regulations for clinical study sites, core laboratories, and other participants, and perform regular site monitoring to assure compliance with them.
Adverse event and device deficiency reporting by the Sponsor will be done following local regulations. Safety reporting will be further specified in the Safety Management Plan.
Periodic reports will be generated and sent to IRBs/ECs and regulatory authorities, as required.
Perform site monitoring of clinical data at the clinical study sites.
SafeHeal retains ownership of all clinical data generated in this study and controls the use of the data for purposes of regulatory submissions to European countries, to the U.S. and/or other governments.
SafeHeal will release study results, regardless of the outcomes, for publication. Investigators will work together to develop publication plans and resulting publications. Additionally, 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. Note that if the study is terminated early, SafeHeal will hasten the release of the results.
SafeHeal contracts with participating institutions/investigators through a Clinical Trial Agreement that defines the scope and responsibilities and associated compensation related to carrying out the obligations under the clinical study.
SafeHeal may seek Medicare coverage for routine costs in this clinical trial. Medicare beneficiaries may be affected by the device under investigation. The study results are expected to be generalizable to the Medicare beneficiary population for the following reasons:
The risk of colorectal cancer increases with age. The median age at diagnosis for colon cancer is 68 years in men and 72 years in women, and for rectal cancer the median age at diagnosis is 63 years in both men and women.[40]

As discussed in Section 0, the SAFE-1 Study (NCT03352570), a multicenter, open label, feasibility study of the Colovac device, enrolled 15 patients. Ten (67%) of the enrolled subjects were men and 5 (33%) were women. The mean age was 59 years and 5 (30%) of the subjects were greater than 65 years old.

Jayne et al reported results for patients undergoing resection for rectal cancer like the subjects in this study. Thus, the subject populations are expected to be similar. Jayne et al. reported an average age of 65.5 years for the men (67.9% of the subjects) and 64.5 years for the women (32.1% of the subjects).[41]

INVESTIGATOR RESPONSIBILITIES

The Principal Investigator is responsible for ensuring the investigation is conducted according to all signed agreements by the study team. 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 Principal Investigator and study staff must adhere to 21 CFR 812 and ISO14155:2020.

The investigator must submit the study protocol to his/her Ethics Committee or IRB 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 or IRB, such as regular reporting, study timing, etc.

Part of the Ethics Committee or IRB approval must include approval of an Informed Consent text specific to the trial. The investigator or his staff must administer this approved Informed Consent text to each prospective study subject, and obtain the subject'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 IRB/IEC 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
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.

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 an electronic form but must be made available for monitoring by the Sponsor or monitor.

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.

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:

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;
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;
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 occurring 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.

INFORMATION PROVIDED BY THE CLINICAL INVESTIGATION SITE

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:

  Seriousness

  Severity of the event

  d. Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  e. Moderate: minimal, local or noninvasive intervention indicated; limiting
  f. Severe: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling

  iii. Life-threatening: urgent intervention indicated, disabling
  iv. Fatal: death related to AE

  Relationship of the event to the investigational device (Not related, possible, probable or causal [definite] relationship).

  Relationship of the event to the index procedure (Not related, possible , probable or causal [definite] relationship)

  If not related to study device or study procedure, causality with

  disease under study

  lack of performance of the investigational device or comparator/worsening of treated condition

  medical history (current/past)

  concomitant or previous medication

  technical issue of the other products used

other (specify)

In addition, the severity of the event will be assessed using a Clavien-Dindo Classification as discussed in Section 0.

Table 11 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 11: 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)
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 IRB or 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

INSTITUTIONAL REVIEW BOARD / ETHICS COMMITTEE & NATIONAL COMPETENT AUTHORITIES

Institution Review Board (IRB) / 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.

The study has been publicly registered prior to enrollment of the first subject in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki on http://clinicaltrials.gov (NCT#05010850).

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

MONITORING PROCEDURES

GENERAL PROCEDURES

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:

Hart Clinical Consultants, LLC
P.O. Box 202
Deland, FL 32721-0202

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 for 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.

SITE QUALIFICATION VISIT

During the site evaluation or Site Qualification process, SafeHeal or SafeHeal representatives will review the protocol and regulatory requirements with the investigator and/or clinical site personnel and will assess if the site meets pre-defined requirements, has the experience, the time and resources to conduct the study.

SITE INITIATION VISIT

Site Initiation Visits will be conducted for sites participating in this trial for training to ensure that protocol-related activities will be conducted in compliance with this protocol. SafeHeal or SafeHeal representatives will provide clinical study training on the protocol, informed consent process, data collection tools, and regulations to the involvement of personnel conducting clinical study activities and investigator responsibilities.

MONITORING VISIT

During a Monitoring Visit, the monitor will perform source data verification by review of original subject documents. To do this, the monitor must have direct access to original source documentation, certified copies of the original source must be provided, or supervised access in situations where direct access is not possible. It will be verified whether signed and dated Informed Consent Forms have been obtained from subject(s)/legal guardian before any clinical-study-related procedures are undertaken. In addition, the monitor will perform routine reviews of study-related regulatory documents and work to secure compliance should any deficiencies be observed.

FINAL MONITORING VISIT / CLOSURE VISIT

Final monitoring visits at the sites will be conducted at the closure of the study. The purpose of the final visit is to collect all outstanding study data documents and materials, ensure that the principal investigator's files are accurate and complete, review record retention requirements with the principal investigator, make a final accounting of all study supplies shipped to the site, provide for appropriate disposition of any remaining supplies and ensure that all applicable requirements are met for the study.

MONITORING REPORTS

After each monitoring visit, the monitor will send the principal investigator a letter summarizing the monitoring visit. The letter will include the date of the visit, any findings from the visit and action items requiring follow-up by the principal investigator and/or the research staff. The principal investigator will be responsible for ensuring that follow-up actions needing attention are resolved at the site and completed in an accurate and timely manner.

COMPLIANCE

This study will be performed in accordance with the last applicable World Medical Association Declaration of Helsinki, ISO 14155:2020 and any applicable local requirements. Additionally, this study will comply with the following FDA Regulations pertaining to the Investigational Device Exemptions (IDE):

21 CFR 812 - Investigational Device Exemptions
21 CFR 50 - Protection of Human Subjects

21 CFR 56 - Institutional Review Boards

21 CFR 54 - Financial Disclosure by Clinical Investigators

21 CFR 58 – Good Laboratory Practice for Nonclinical Laboratory Studies

21 CFR 820 - Quality System Regulation

PARTICIPATING INVESTIGATORS AND INVESTIGATION SITES

The sponsor will maintain an updated list of principal investigators, investigation sites, and institutions. This list will be kept separately from the protocol.

PROTOCOL AMENDMENTS

Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor. All modifications to the study will be submitted by Sponsor or designee to the IRB/IEC and the relevant competent authority (where required) for authorization or notification according to the national regulations. Once the protocol has been approved, it will be signed and dated by the investigator for acknowledgement. Protocol amendments must not be implemented without required approvals.

TRIAL DISCONTINUATION AND COMPLETION

TRIAL DISCONTINUATION

This trial may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Terminating parties may include: the Sponsor, DSMB, IRB/IEC, or regulatory authorities. Written notification, documenting the reason for trial suspension or termination, will be provided by the suspending or terminating party to the Study Sponsor, Investigators, IEC/IRB and regulatory authorities, as applicable. Trial subjects will be contacted, as applicable, and be informed of changes to trial visit schedule.

The trial may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB/IEC and/or Regulatory Authorities.

TRIAL COMPLETION

The trial is considered completed with the last visit/contact of the last subject participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) when all queries have been resolved and all required data has been monitored.

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