Short versus long interval to loop ileostomy reversal after ileal pouch surgery in patients with ulcerative colitis (SLIRPS) trial

A randomized, prospective trial investigating the timing of diverting ileostomy closure after ileal j-pouch surgery.

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1 SUMMARY

Title:	Short versus long interval to loop ileostomy reversal after ileal pouch surgery in patients with ulcerative colitis (SLIRPS) trial
Research Hypothesis:	In patients with ulcerative or indeterminate colitis who undergo ileal pouch anal anastomosis and diverting loop ileostomy (IPAA) surgery a short interval to loop ileostomy reversal will result in differences in complications and quality of life compared to a long interval to loop ileostomy reversal.
Phase:	III
Study design:	Prospective, randomized, multicenter
Study population:	Adult patients with ulcerative colitis (UC) or indeterminate colitis (IC) who will undergo ileal j-pouch surgery.
Sample size:	126-152 patients
Treatment:	**Phase 1:** • Colorectal excision, ileal j-pouch, & diverting ileostomy surgery **Phase 2:** • Diverting ileostomy closure surgery
Treatment duration:	Phase 1 will have a treatment duration of approximately 6 weeks that will begin after informed consent #1 is obtained and will end within 1 week of ileal j-pouch surgery. Phase 2 will have a duration of approximately 6 months and will begin after informed consent #2 is obtained.
Criteria for inclusion:	• Signed informed consents. • Man or woman between 18 and 64 years of age. • UC or IC diagnosed by routine clinical, radiographic, endoscopic, and pathological criteria. • Patient will be scheduled for non-emergent proctocolectomy or completion proctectomy with ileal j-pouch anal anastomosis

	(IPAA) and loop ileostomy (IPAA). • Clinical assessment of patient after IPAA surgery indicates that patient is suitable for early ileostomy reversal
Criteria for exclusion:	• Age < 18 or > 64 years • Body mass index (BMI) equal or above 40 kg/m2 • Crohn's disease or suspected Crohn's disease • Known previous or concurrent malignancy (other than that considered surgically cured, with no evidence for recurrence for 5 years). A recent history of basal cell or squamous cell carcinoma does not exclude the subject. • Pregnant patients and female patients who do not satisfy the standard of care requirements of participating centers for an elective surgical procedure. • Hemodynamic instability (persistent pulse rate < 50 or > 120 bpm, systolic blood pressure < 90 or > 160 mm Hg, uncontrolled cardiac arrhythmia, or active vasopressor drug use) • Systemic sepsis • Organ transplant recipient (e.g. Liver, Kidney, Pancreas) • Immunosuppression due to chemotherapy drug use or systemic disease. • Prednisone dose > 20 mg per day (or equivalent other steroid dose) within 4 weeks of scheduled IPAA • Patients with ongoing C. difficile colitis • Patients with pre-existing hepatic disease and portal hypertension • Patients with pre-existing renal dysfunction (creatinine >1.7 mg/dl) • Patients with poorly controlled pre-existing chronic lung disease • Therapeutic anticoagulation or coagulopathy (PTT or INR above normal range) • Blood Hemoglobin < 8 g/dl • Serum Albumin < 2.5 g/dl • Clinical assessment of patient after IPAA surgery indicates

	that patient is not suitable for early ileostomy reversal • Participation in another clinical IBD drug trial within the last 30 days, or simultaneous participation in another clinical trial • Well-founded doubt about the patient's cooperation • Individualized decision by the surgeon to exclude the patient based on sound surgical judgment
Criteria for Evaluation:	A confirmed or presumed diagnosis of ulcerative or indeterminate/undetermined colitis will be determined by the study surgeons. The diagnosis will be based on the constellation of clinical, endoscopic, and pathology results that are used in routine practice to establish a diagnosis of these conditions.
Primary variables	Comprehensive Complication Index at 6 months after randomization.
Secondary variables:	(1) Total number of postoperative complications per patient; (2) Percent of patients with complications; (3) Total number of stoma related complications per patient; (4) Health-related quality of life; and (5) IPAA functional outcomes (all at 6 months after randomization).
Statistical analysis:	A Consort Diagram will be used to account for all patients screened for inclusion in the trial; those who were excluded and included and reasons for exclusion; those who were randomized; and those who were followed at each time point or who were lost to follow-up. The primary analysis will be by intention-to-treat, meaning that the patients will be analyzed by the group to which they were randomized. This means that patients randomized to the short interval closure group who have postoperative complications that delay closure will still be analyzed in the group to which they were randomized. Secondary analyses will be done per-protocol (analyzing patients who followed the protocol), and as-treated (analyzing patients by the treatment they actually received). Patient baseline characteristics will be compared between the early and late closure groups using a chi-square test for categorical variables and a t-test for independent samples for normal continuous variables or a Wilcoxon two sample ranks test for non-normal continuous variables. Complications will be reported using the Clavien-Dindo classification. Perioperative details in the two groups will be compared using the same methods as were used for comparing the

	patient baseline characteristics. The primary analysis will be comparing Comprehensive Complication index and overall complication rates up to 6 months postoperatively between the two randomized groups using a generalized linear model with a log-link function with group (short vs. long interval closure) and hospital as the independent variables. We will also include any patient baseline characteristics that remained unbalanced in spite of randomization. Secondary analyses will include a comparison of mean number of complications per patient using a zero-inflated Poisson model, and a comparison of severe complications (Clavien-Dindo Grade IIIa or higher) using the same methods as were used for the primary analysis. We will also compare the mean number of stoma related complications using a zero-inflated Poisson model. Since the quality of life scales are continuous variables measured over time, we will compare the early vs. late closure groups for these outcomes using linear mixed models.
Duration of study	Duration per patient will be approximately 7 months. The anticipated time of the overall study duration is approximatly 18 months
Number of centres:	17-25 centers in United States

2 INTRODUCTION AND BACKGROUND

Ulcerative colitis (UC) and indeterminate colitis are chronic inflammatory gastrointestinal disorders, which are limited to the colon and characterized by the involvement of the mucosa only (in contrast to the transmural inflammation seen in CD). UC primarily affects young adults (20 - 40 years) but may present also at a very early age (5-10 years) or in later in life (>60 years). The inflammatory process in UC and IC is primarily localized to the rectum (proctitis) or can extend proximally in a contiguous manner involving the mucosa up to the splenic flexure (left sided colitis) or involving the entire colon (extensive colitis). A key clinical feature of UC and IC is bloody diarrhea. The clinical course of UC and IC is characterized by periods of spontaneous exacerbation (acute flares) and remission (50 - 80% of patients) while some patients have a continuous active disease course (15 - 30% of patients) and others develop severe colitis (5 - 10% of patients), which can result in colectomy if medical therapy is not effective. Long standing UC and IC is associated with an increased risk of colorectal cancer; the use of 5-ASA products may reduce this risk. UC and IC can also be associated with inflammation involving extra-intestinal sites such as the skeletal, skin, or biliary system.

A “defunctioning” loop ileostomy is routine to the practice of colorectal surgery. In general, this type of ileostomy is put in place to direct the enteric contents away from a newly created surgical anastomosis that is downstream (distal) to the ileostomy. For example, a defunctioning loop ileostomy is routinely made during ileal pouch anal anastomosis (IPAA) surgery to facilitate healing of the IPAA. It is common practice to leave the diverting ileostomy in place for 8 to 12 weeks with the idea that this interval is needed to ensure complete healing of the anastomosis. After 8 to 12 weeks, an imaging study (e.g. contrast enema) is performed to confirm complete healing of the anastomosis. After that, so long as healing of the anastomosis has occurred, the diverting ileostomy is surgically reversed. While potentially beneficial to the healing process, a diverting ileostomy may also be detrimental to the health and well-being of the patient. Potential detriments include dehydration, leakage from the ileostomy with resultant skin irritation and interference with activities of daily living, ileostomy dysfunction, and its negative impact on both physical and emotional function and quality of life. In an ideal situation, the diverting ileostomy would be left in place for an adequate period to facilitate healing of the anastomosis, while closing the ileostomy at the earliest appropriate time point in order to minimize the risks associated with an ileostomy.

The primary outcome variable for the study will be the Comprehensive Complication Index (CCI). The CCI is a novel continuous scale to measure surgical morbidity that has been developed in the past few years. (Slankamenac, 2013) It is based upon a survey of patients, nurses, and surgeons measuring their perceptions of the seriousness of 30 postoperative complications common in abdominal surgery (Slankamenac, 2011). From this survey, a score between 0 (no complications) and 100 (death) was developed to measure the occurrence of one or more

postoperative complications in abdominal surgery patients, taking into account the number and seriousness of the complications. The score has been validated using four different methods (K. Slankamenac, 2013), and has been applied to the databases from 3 different randomized surgical trials and shown to be useful in reducing required sample sizes in surgical clinical trials (K. Slankamenac, 2014)

Quality of life and functional outcomes of IPAA in patients with ulcerative colitis have been evaluated in retrospective studies. (Delaney 2003, Farouk 2000) The SF-12 is a validated quality of life measurement tool that has been used to evaluate patients who have undergone colorectal resection.

JUSTIFICATION AND OBJECTIVES OF THE CLINICAL TRIAL

Randomized prospective trials have evaluated the outcomes of standard (8 weeks) and decreased (8-13 day) intervals to defunctioning ileostomy reversal after rectal cancer surgery and have demonstrated superiority of decreased interval to closure. [Danielsen 2017; Alves 2008] The unique significance of our study is that it will focus on ulcerative colitis patients who undergo ileal pouch surgery with temporary defunctioning ileostomy.

This operation is performed on a minimum of 15 patients, with UC or IC, annually at University of Colorado Hospital and at the co-investigator centers. This surgery is performed by fellowship-trained and board certified colorectal surgeons at the University of Colorado.

Hypothesis: In patients with ulcerative or indeterminate colitis who undergo ileal pouch anal anastomosis and diverting loop ileostomy (IPAA) surgery* a short interval to loop ileostomy reversal will result in differences in complications and quality of life compared to a long interval to loop ileostomy reversal.

*For clarification, please see illustrations and images at end of this document

Aim #1: To compare the Comprehensive Complication Index (CCI), the incidence of postoperative complications, including total number of complications per patient, percent of patients with complications, and total number of ostomy-related complications per patient among IPAA patients who have their ileostomy reversed after a short interval compared to a long interval.

Aim #2: To compare the short vs. long interval groups on measures of health-related quality of life (SF-12) and IPAA functional outcomes

3 PATIENT SELECTION

Inclusion criteria

- Signed informed consent
- Patient age 18 to 64 years
- Confirmed or presumed diagnosis of ulcerative colitis or, indeterminate/undetermined colitis*
- Patient will be scheduled for non-emergent proctocolectomy or completion proctectomy with ileal j-pouch anal anastomosis (IPAA) and loop ileostomy (IPAA).
- Clinical assessment of patient after IPAA surgery indicates that patient is suitable for early ileostomy reversal

Exclusion criteria

Patients who meet one of the following criteria are to be excluded from the trial:

- Age < 18 or > 64 years
- Body mass index (BMI) equal or above 40 kg/m2
- Crohn's disease or suspected Crohn's disease
- Known previous or concurrent malignancy (other than that considered surgically cured, with no evidence for recurrence for 5 years). A recent history of basal cell or squamous cell carcinoma does not exclude the subject.
- Pregnant patients and female patients who do not satisfy the standard of care requirements of participating centers for an elective surgical procedure.
- Hemodynamic instability (persistent pulse rate < 50 or > 120 bpm, systolic blood pressure < 90 or > 160 mm Hg, uncontrolled cardiac arrhythmia, or active vasopressor drug use)
- Systemic sepsis
- Organ transplant recipient (e.g. Liver, Kidney, Pancreas)
- Immunosuppression due to chemotherapy drug use or systemic disease.
- Prednisone dose > 20 mg per day (or equivalent other steroid dose) within 4 weeks of scheduled IPAA
- Patients with ongoing C. difficile colitis
- Patients with pre-existing hepatic disease and portal hypertension

- Patients with pre-existing renal dysfunction (creatinine >1.7 mg/dl)
- Patients with poorly controlled pre-existing chronic lung disease
- Therapeutic anticoagulation or coagulopathy (PTT or INR above normal range)
- Blood Hemoglobin < 8 g/dl
- Serum Albumin < 2.5 g/dl
- Clinical assessment of patient after IPAA surgery indicates that patient is not suitable for early ileostomy reversal
- Participation in another clinical trial within the last 30 days, or simultaneous participation in another clinical trial
- Well-founded doubt about the patient's cooperation
- Individualized decision by the surgeon to exclude the patient based on sound surgical judgment

Overview of time sequence

1. **PHASE 1 (-30 to 0 days): Screening Visit and Informed Consent #1:** Assessment and documentation of initial inclusion and exclusion criteria will occur during the IPAA preoperative assessment clinic visit. A brief oral and written description of the trial will be presented to subjects who satisfy the initial inclusion/exclusion criteria and express interest in participation. These patients will be asked to review and sign informed consent #1 for SLIRPS trial participation. Case report form-1 (CRF-1, screening) will be completed at this time. The assessment will be performed by the study surgeon or study assistant at each site.

2. **PHASE 1 (day 0): IPAA Surgery (See Illustrations at end of protocol):**
   a. The use of a mechanical and/or oral antibiotic bowel preparation will be the discretion of the study surgeon, and will be documented in the appropriate study form. The same will apply to the preoperative use of intravenous prophylactic antibiotics and venous thromboembolism prophylaxis. "pre-IPAA" data points of interest will be recorded in CRF 2 by the study surgeon or trial assistant within 3 days of IPAA surgery.
   b. The IPAA surgery, including ileostomy creation, will be performed by the study surgeon in a manner that is consistent with accepted and standard surgical practice. The use of laparoscopic, hand-assisted laparoscopic, robotic, open, or other surgical techniques will be at the discretion of the study surgeon and will be recorded in CRF-3 (IPAA surgery details) by the study surgeon or trial assistant within 3 days of the IPAA surgery.

3. **PHASE 1 (day 5 to 12): IPAA Clinical Assessment:** On day **5-12** after IPAA surgery, the surgeon performs a routine "clinical assessment" of the patient and determines if the patient is suitable or not suitable for early ileostomy closure. (CRF 4, IPAA Assessment).
    a. Study patients judged not suitable for early ileostomy closure are excluded from the study. Documentation of the reasons for "unsuitability" will be captured on CRF-4 (IPAA assessment).
    b. Study patients judged suitable for early ileostomy closure will be asked for informed consent to participate in the trial.

4. **PHASE 2 (day 5 to 12): INFORMED CONSENT #2:** Study patients judged clinically suitable, by the study surgeon, for early ileostomy closure, will be ask to review and sign informed consent #2 for SLIRPS trial participation. Oral and written description of the trial will be presented to subjects who satisfy the inclusion criteria and initial and secondary exclusion criteria and express interest in participation. Consent will be obtained by the study surgeon or assistant at each site. After informed consent is obtained, the patient will be registered into the trial.

5. **PHASE 2 (day 5 to 12): IPAA Radiological Assessment** will be performed on **day 5-12** after IPAA <u>on all study patients who are determined by the study surgeon to be clinically suitable for early ileostomy closure</u> and who have provided informed consent (#1 and #2) to participate in the trial.
    a. Radiologic assessment will be performed at day **5 to 12** after IPAA ostomy surgery. CT or fluoroscopic imaging of the IPAA with a water-soluble contrast medium will be performed to visualize the IPAA and determine the presence of radiologic leak. With either imaging modality, the enema contrast medium is instilled using a soft catheter.
    b. **Subjects not radiologically suitable for early ileostomy reversal:** Study patients with a radiological leak from the IPAA will **not be randomized** to early or late closure. Details of the radiologic leak will be captured in CRF-4 (IPAA assessment). The patient will not be randomized to control or experimental trial arms. Treatment of these patients will follow the standards of care.
    c. **Subjects radiologically suitable for early ileostomy reversal:** Study patients with no radiologic leak from the IPAA will be randomized to the control or experimental study arms. (CRF-4)

6. **PHASE 2 (day 5 to 12): <u>RANDOMIZATION</u>:** Immediately after IPAA <u>radiologic</u> assessment, study patients with no radiologic leak will be randomized to early (post-IPAA day 7 to 12) or late (post-IPAA ≥ 8 weeks) ileostomy closure via the REDCap data collection system. The randomization scheme will be established by the study biostatistician. The randomization will be stratified by study site. Within each site, randomly

selected block sizes of 2, 4, or 6 will be used so that the site investigators cannot predict beforehand the group to which the patient will be randomized.

7. **PHASE 2 (day 7 to 12 or week 8-12): Ileostomy Closure:**
    a. Early ileostomy closure will be performed at 7 to 12 days after IPAA.
    b. Late ileostomy closure will be performed 8 - 12 weeks after IPAA.
    c. The ileostomy closure surgical technique is at the discretion of the surgeon.
    d. CRF-5 (ileostomy reversal details) will be completed within 3 days of ileostomy reversal surgery.
    e. Endoscopic examination (optional): Rigid and/or flexible endoscopic examination of the IPAA may be performed per standard practice/standard of care, including non-study-related informed consent, at the discretion of the study surgeon following standard of care. (CRF-5)

8. **PHASE 2 (day 7 – 12 to 6 months): Outcome assessment:**
    a. The Comprehensive Complication Index and postoperative complications will be assessed and recorded by the study surgeon or trial assistant after review of the medical record, conversation with patient, and members of the care team (when appropriate). This assessment and documentation will begin immediately after randomization is performed and will be updated at 1-2 month intervals until 6 months after randomization. (CRF-6)
    b. Functional outcomes and quality of life (CRF-7)**:** IPAA functional outcomes and quality of life (SF-12) will be assessed and recorded once at 6 months <u>after ostomy reversal</u>.

4 DESCRIPTION OF THE CLINICAL TRIAL SEQUENCE

Screening visit

Data to be recorded:

<u>General parameters:</u>

- Initials
- Age
- Gender
- ASA
- BMI
- Hemoglobin (g/dl)

- Serum Albumin (g/dl)
- Active smoker (smoking within 1 month of IPAA)
- Bowel Preparation (choose: none, mechanical only, oral antibiotic only, mechanical AND oral antibiotic)Date of birth

Case history

Medication Use

- Anti TNF drug use within 8 weeks of IPAA surgery date
- Steroid use within 4 weeks of IPAA surgery date (excluding Budesonide)
- Vedolizumab drug use within 8 weeks of IPAA surgery date
- Other colitis drugs (e.g. methotrexate, azathioprine, 5-ASA) within 4 weeks of IPAA surgery date

Examinations

- Vital signs: blood pressure (mm Hg), heart rate (min^{-1}), weight (kg), calculation of BMI
- Physical examination: Routine preoperative examination
- Blood draw: blood hemoglobin, serum albumin, other blood tests at discretion of surgeon

Formal aspects:

Informed consent procedure

Verification of inclusion / exclusion criteria (eligibility check), as far as possible

PHASE 1, IPAA Surgery

IPAA surgery type

- Proctocolectomy with IPAA (2-stage procedure)
- Completion proctectomy with IPAA (3-stage procedure)

Indication for proctocolectomy or colectomy

- Colitis symptoms inadequately controlled by medical therapy or steroid-dependence
- Colorectal epitheial dysplasia

Urgency of colectomy or proctocolectomy

- Urgent (colectomy or proctocolectomy performed on a hospitalized patient)
- Elective (colectomy or proctocolectomy performed on a patient who was not hospitalized on the day before surgery)

IPAA Surgery Details

- Duration of surgery (cut to close, minutes)
- Open removal of colon and rectum
- Laparoscopic proctocolectomy
- Laparoscopic colectomy with open proctectomy
- Hand assisted laparoscopic (HAL) proctocolectomy
- HAL colectomy colectomy with open proctectomy
- Robotic proctocolectomy
- Robotic colectomy with open proctectomy
- Lap, HAL, or Robotic proctocolcetomy or colectomy with unplanned conversion to open surgery
- Trans-anal-trans-abdominal IPAA
- Stapled IPAA
- Sutured IPAA
- IPAA anastomotic leak test performed (yes/no)
- IPAA anastomotic leak test result: no leak, small leak, big leak
- Ileal pouch bleeding that required suture placement or other methods to stop bleeding
- IPAA tension (none, minimal, moderate)
- EBL
- Injury to surrounding structures (specify, enterotomy, ureter injury, pelvic hemorrhage, etc.)
- Sepra Film wrap of ileostomy
- Epidural anesthesia

PHASE 1: IPAA Clinical Assessment

- Post-IPAA day that clinical assessment was performed
- Review / confirmation of inclusion exclusion criteria

- Informed consent #2 obtained (only for patients determined to be clinically suitable for early ileostomy reversal)
- Not ready ileostomy reversal (explanation-comment and Clavien Dindo classification if applicable)

PHASE 2: IPAA Radiological Assessment

- Post-IPAA day that radiologic assessment was performed
- CT with rectal contrast (yes or no)
- Contrast enema (yes or no)
- Radiologic exam OK (Yes or No)
- Randomization to early or late ileostomy closure study arms
- Radiologic exam not OK and patient will NOT be randomized to experimental or control trial arms (explanation required)
- Explanation for no randomization
- Radiologic leak (yes or no, if yes, Clavien-Dindo classification if applicable)
- Other reason for no randomization

PHASE 2: Ileostomy Closure

- Duration of surgery (cut to close, minutes)
- Stapled ostomy closure
- Sutured ostomy closure
- Ostomy site skin complete closure
- Ostomy site skin partial closure (e.g. pursestring)
- Ostomy site skin not closed
- Endoscopic examination of IPAA (no, yes, comments)

PHASE 2: Outcome Assessment

- IPAA stenosis requiring more than simple digital dilation
- Small Bowel Obstruction (imaging confirmed)
- Ileus

- Venous Thromboembolism
- Lung or Heart-related complications
- Hemorrhage requiring transfusion
- high output ileostomy
- Peristomal skin irritation
- Peristomal infection
- ileostomy prolapse
- ileostomy stenosis
- ileostomy revision necessary
- ileostomy leakage
- ileostomy dusfunction

Readmission

- Total # of inpatient hospital days
- Total # of hospital admissions

Comprehensive Complication Index: web-based calculation

5 ADVERSE EVENTS

Definitions

Adverse events (AEs)

Adverse events (AEs) will be recorded at each regular scheduled study visit or study phone contact in the patient record (source document) as well as on a specific AE form on the electronic CRF.

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product, e.g.:

- any new diagnosis
- any symptom that requires medical clarification or leads to in-patient admission (surgery or accident)
- any suspected adverse drug reaction (ADR)
- any symptom that appears on the patient's medical records
- any event related in time with the application of the study medication and affecting the health of the patient (including laboratory value changes)

Serious Adverse Events (SAE)

A serious adverse event (experience) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity

Non-serious adverse events are all AEs that do not fall into any of the above categories.

Expected Adverse Events (i.e. complications of procedures; definitions included):

- Wound infection: redness or purulence at the IPAA incision that required opening of the wound and or treatment with antibiotics
- Abdominal or pelvic abscess: abnormal abdominal or pelvic fluid collection detected by CT or other imaging in a patient with clinical evidence of infection
- IPAA radiologic leak: free or contained extravasation of luminal contrast from the IPAA in a patient without clinical signs of IPAA leak
- IPAA clinical leak: free or contained extravasation of luminal contrast from the IPAA in a patient with clinical signs of IPAA leak
- IPAA stenosis: more than a simple web that can be treated by digitation
- Small bowel obstruction (SBO): radiologic confirmed in a patient with clinical signs of SBO
- Ileus: inability to tolerate normal oral intake by 72 hours after IPAA or ostomy reversal and/or radiologically confirmed in a patient with clinical signs of ileus
- Venous Thromboembolism: new diagnosis of upper or lower extremity of mesenteric vein VTE or pulmonary embolism after IPAA or ostomy reversal

- Lung or heart-related complications: include new diagnosis of cardiac arrhythmia, coronary artery disease, congestive heart failure, pneumonia, pneumonitis after IPAA or ostomy reversal
- Hemorrhage requiring transfusion: pRBC administered after IPAA or ostomy reversal
- High output ileostomy: Regular use of antiperistaltic drugs required to control ileostomy output volume
- Peristomal skin irritation: irritation of the peristomal skin that resulted in pain, interference with activities of daily living (ADL), or unplanned treatments
- Peristomal infection: peristomal cellulitis or abscess requiring incision and drainage or unplanned ostomy surgery or antibiotic therapy
- Ileostomy prolapse: ileostomy prolapse that interferes with ileostomy pouching and/or ADL or requires surgical treatment
- Ileostomy stenosis: ileostomy stenosis that causes ileostomy dysfunction and/or interferes with ADL or requires surgical treatment
- Ileostomy revision necessary: unplanned ileostomy surgical treatment required
- Ileostomy leakage: persistent or recurrent ileostomy appliance leakage that interferes with ADL and requires more than ordinary measure to control
- Ileostomy dysfunction: dysfunction of the ileostomy that causes extraordinary problems with output, pouching, intestinal blockages, or otherwise interferes with ADL more than is usual and expected.
- Reoperation: any unplanned reoperation within 6 months of IPAA surgery
- Readmission: Any unplanned hospital readmission within 6 months of IPAA surgery
- Postoperative complication occurrence will be assessed via medical record review, discussion with study surgeon, other care givers, and study patient and recorded (CRF-6) at an interval of every 1 month until 6 months after randomization. Postoperative complication severity will be scored according to the Clavien-Dindo (CD) classification of surgical complications (Dindo, 2004, **Table**) The Comprehensive Complication Index will be calculated for each patient at 6 months after randomization.

6 DOCUMENTATION AND REPORTING OF ADVERSE EVENTS

All adverse events will be treated at the discretion of each individual center. All adverse events will be followed to resolution or until determined to be permanent. Adverse events will be graded using the definitions below:

Grade 1: Mild asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate, minimal, local or noninvasive symptoms with intervention indicated; limiting age-appropriate instrumental ADLs (Activities of Daily Living).

Grade 3: Severe or medically significant symptoms but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Serious Adverse Events: All information regarding SAEs will be collected and recorded on a specific SAE form. To ensure patient safety, each SAE must also be reported to the University of Colorado, within 24 hours of learning of its occurrence.

An SAE is defined by an undesirable sign, symptom or medical condition defined as an event which is:

1. Fatal or life-threatening
2. Results in persistent or significant disability/incapacity
3. Requires inpatient hospitalization
4. Constitutes a congenital anomaly/birth defect,
5. Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

The following has to be documented for each AE:

- Nature of the event
- Time of onset: date, time
- Concomitant treatment: product (generic name), indication, dosage, dosage interval, presentation, mode of administration, administration regimen
- Duration of the AE

- Severity
- Seriousness
- Causality
- Outcome

Severity

The severity is evaluated as follows:

1. Mild: - event/symptom does not interfere with normal daily activities
2. Moderate: - event/symptom interferes with normal daily activities
3. Severe: - event/symptom prevents normal daily activities

Causality

The relationship between an AE and the research is classified by the following:

Certain

A clinical event, including laboratory test abnormality, is occurring in a plausible time relationship to the research, and which concurrent disease or other drugs or chemicals cannot explain.

Probable/Likely

A clinical event, including laboratory test abnormality, with a reasonable time sequence to the research , unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response. **Possible**

A clinical event, including laboratory test abnormality, with a reasonable time sequence to the research, but which could also be explained by concurrent disease or other drugs or chemicals. **Unlikely**

A clinical event, including laboratory test abnormality, with a temporal relationship to the research which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Conditional/Unclassified

A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are under examination.

Not assessable / Unclassifiable

A report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Not related

There is sufficient information available to show that the eventis unrelated to the research.

The **course and outcome** of the adverse event will be commented on as follows:

1) Recovered without sequelae
2) Not yet recovered
3) Recovered with sequelae
4) Fatal

Documentation and Reporting of Serious Adverse Events

On enrolment in the study, the patients will be instructed to contact the investigator if a serious or unexpected AE occurs, so that appropriate measures can be taken.

Any SAE (including death, irrespective of the cause) occurring during or for up to 14 days after the end of the study must be reported without delay, i.e. within five days, by telephone and by fax to the principal investigator of the study organization or his designee, irrespective of its relationship with the research(minimum information required: investigator's name/study center, patient number, patient initials, date of first dose, date of last dose, date of event, description of event, causality assessment, and countermeasures).

Address:	**Principal investigator**	Phone: 303 724-2728
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Aurora, CO 80045		

A specific AE documentation form will be provided to the investigators (see appendix). In case of an SAE, this should be completed by the physician as an initial report, and sent (via fax) to the principal investigator. The report must contain a detailed description of the symptoms observed and the concomitant treatment administered. Furthermore, the investigator must comment on a possible causative relationship between the AE and the trial medication. Each SAE must be followed until it is resolved or can be explained satisfactorily.

In accordance with drug safety and national requirements, the study PI will inform the Data and Safety Monitoring Board (DSMB) of the study and will make sure that the involved persons will obtain adequate information. Also the local principal investigator will inform the local Ethics Committee.

The following instructions must be heeded:

In the case of an intolerable SAE, the patient must, at the decision of the investigator, be withdrawn from the clinical trial, and symptomatic treatment must be administered. The measures taken must be recorded on the electronic CRF.

In accordance with local legislation, the investigators will submit copies of the final SAE-report to the Regulatory Authorities concerned, if necessary.

7 WITHDRAWAL OR STOP OF STUDY CRITERIA

Criteria in individual cases

Any patient can withdraw from the study at any time without personal disadvantages and without having to give a reason. The time of withdrawal, the results available up to that time, and, if known, the reason for withdrawal must be documented on the electronic CRF.

The investigator can also discontinue the study after considering the risk-to-benefit ratio, if he/she no longer considers the further participation of the patient justifiable. The date of and the primary reason for the withdrawal as well as the observations available at the time of withdrawal are to be documented on the electronic CRF.

Reasons leading to the **withdrawal** of a patient can include the following (primary reason must be determined):

- inclusion criterion not fulfilled or exclusion criterion fulfilled; coming to knowledge after recruitment
- patient's request
- technical or logistical reasons (e.g. a change in place of residence, not referred by family physician, etc.)
- other reasons (noting reason)

Criteria for the termination of the whole study

If serious safety concerns arise, the coordinating investigator can terminate or interrupt the study by agreement with the sponsor. If new information on the risk-to-benefit ratio of the treatment methods used in the study is obtained in the meantime, the coordinating investigator reserves the right to interrupt or terminate the project by agreement with the sponsor. Premature termination is also possible if the coordinating investigator, or the investigators and the sponsor if patient recruitment is insufficient and cannot be expedited by appropriate measures.

8 DATA SAFETY MONITORING

Data Safety Management Board: An independent Data and Safety Monitoring Board (DSMB), comprised of 2 independent surgeons and 1 biostatistician, has been established and will meet at the start of the study and at months 6 and 12 after enrollment begins. The chairman and site investigators will be masked to study outcomes during the course of the trial. Only the study biostatistician and DSMB members will have access to the study outcomes for monitoring purposes during the course of the study.

Stopping Endpoints: At their first meeting, the DSMB will decide how they wish to monitor the study. Typically, a DSMB will monitor all aspects of a study to ensure its scientific integrity, including patient screening and accrual, follow up, performance of individual centers, data acquisition and quality issues, adverse events, and outcomes. At the first meeting, we will also determine their desire in establishing formalized stopping rules. Any data presented by treatment group at the DSMB meeting will be blinded with regard to the identity of the comparison groups, and participating investigators (except for the study biostatistician) will not see any data broken down by treatment group during the course of the trial.

9 RANDOMIZATION, DATA MANAGEMENT AND DATA MONITORING

The randomization of the patients and the processing and analysis of the data will be carried out by the lead study biostatistician (William Henderson, PhD) at University of Colorado. The randomization will be stratified by study site. Within each site, randomly selected block sizes of 2, 4, or 6 will be used so that the site investigators cannot predict beforehand the group to which the patient will be randomized.

Data collection will be performed using REDCap (Research Electronic Data Capture). REDCap is a secure web application for building and managing online surveys and databases. The software is available at no cost for REDCap Consortium Partners. The building of an online survey or database and the inputting of data can be done anywhere in the world over a secure web connection with authentication and data logging. The REDCap surveys and databases can be used by researchers from multiple sites and institutions. Confidentiality will be protected. REDCap is considered “Part 11 capable”, meaning that the software has all the required features for compliance.

We have built a REDCap database for this study using 8 forms per patient. These will include Form 1, Screening; Form 2, Pre-IPAA Data; Form 3, IPAA operative Details,; Form 4, IPAA Assessment; Form 5, ostomy reversal details; Form 6, Complications; Form 7 – Functional Outcome & SF-12; Form 8, Adverse Events.

Study data for this study will be collected and stored using electronic records. Data captured will be entered in real time at each clinical site using web forms developed to replicate paper case report forms. All data will be created, modified, maintained, archived, retrieved and distributed by a computer system**.** The use of electronic records will increase the speed of data collection and exchange. This will reduce the manpower necessary to perform double-data entry from paper forms and transcription error. In addition, electronic records permit economical storage of study data and ease of accessibility and analysis. Data management and data quality systems will be built into the system.

Data quality using electronic records will ensure that data are attributable, legible, contemporaneous and original.

The biostatistics team at the University of Colorado will track the data collection, provide data security, control for confidentiality of study data, maintain computer backups to protect data until study closure and archive study data according to FDA requirements (21 CFR 11). Electronic signatures will be linked to each entry.

All computer systems and programs will be password protected, and all electronic communications of study and other confidential information will be encrypted. Personnel at the CGIBD have extensive training and experience using electronic data systems. Good computer security practice (restricting physical access to machines, prohibition of password sharing, and logging off computers after work hours or when away from the machine) will be required of all study personnel.

Only authorized persons are authorized for data entry and access. Data security systems require password protected identification codes for data entry and provide protection against data manipulation. The database is located on a server protected by firewalls. Access to the database server will not be allowed by users on computers outside of the firewall-protected zone. Virus protection software is installed on each study machine. System access to computer systems will be audited. Redundant backups and off-site backup storage will allow for quick restoration of data in the unlikely event that a hardware failure, disaster, or security breach should occur. Servers and backups will be located in a secured location with access limited to authorized personnel.

Data cleaning will include range and edit checks, cross form edit checks, query generating and tracking and periodic data status reports. Any data errors or inconsistencies detected after data entry will be automatically tracked, communicated and resolved using a web-based application. An audit trail of all data changes over the life of the study will be maintained. All study raw data, forms, documents, software programs, software applications and computer data files will be indexed and archived routinely. Strict version control of documents and software applications will be instituted. Retention of study documentation after study completion will be seven years after closure with the IRB. Standardized study

management reports will be generated monthly during the recruitment phase of the study. These reports will be used to track study progress including patient enrolment, randomization, compliance, patient status changes, and study events. The data will be reported for each Study Center individually and summarized for the study as a whole. A report will also be generated for the DSMB meeting. This report will include additional information on clinical events and adverse events that is coded by blinded treatment group. Other than the study statistician and statistical analyst, no study personnel will see this report.

10 STATISTICAL CONSIDERATIONS

Sample Size Calculation

The developers of the CCI consider a 10-point difference in their 0 to 100 morbidity scale to be clinically meaningful; it reflects a 1-grade difference in the established Clavien-Dindo classification of postoperative complications (Slankamenac, 2014; Clavien, 2009). They also report a standard deviation of the CCI of 20-22 in two surgical trials. Assuming 80% power and an $\alpha = 0.05$ level of significance, our trial would need about 63-76 patients per group, or a total of 126-152 patients to complete both phases of the trial. It is anticipated that up to 600 patients will be required for phase 1 due to the expected ≤ 75% drop out of phase 1 patients who are not eligible for phase 2.

Statistical analyses

A Consort Diagram will be used to account for all patients screened for inclusion in the trial; those who were excluded and included and reasons for exclusion; those who were randomized; and those who were followed at each time point or who were lost to follow-up. The primary analysis will be by intention-to-treat, meaning that the patients will be analyzed by the group to which they were randomized. This means that patients randomized to the short interval closure group who have postoperative complications that delay closure will still be analyzed in the group to which they were randomized. Secondary analyses will be done per-protocol (analyzing patients who followed the protocol), and as-treated (analyzing patients by the treatment they actually received).

Patient baseline characteristics will be compared between the early and late closure groups using a chi-square test for categorical variables and a t-test for independent samples for normal continuous variables or a Wilcoxon two sample ranks test for non-normal continuous variables.

Complications will be reported using the Clavien-Dindo classification. Perioperative details in the two groups will be compared using the same methods as were used for comparing the patient baseline characteristics.

The primary analysis will be comparing Comprehensive Complication index and overall complication rates up to 6 months postoperatively between the two randomized groups using a generalized linear model with a log-link function with

group (short vs. long interval closure) and hospital as the independent variables. We will also include any patient baseline characteristics that remained unbalanced in spite of randomization. Secondary analyses will include a comparison of mean number of complications per patient using a zero-inflated Poisson model, and a comparison of severe complications (Clavien-Dindo Grade IIIa or higher) using the same methods as were used for the primary analysis. We will also compare the mean number of stoma related complications using a zero-inflated Poisson model. Since the quality of life scales are continuous variables measured over time, we will compare the early vs. late closure groups for these outcomes using linear mixed models.

DSMB interim analyses and early stopping rules for interim analyses

At their first meeting, the DSMB will decide how they wish to monitor the study. Typically, a DSMB will monitor all aspects of a study to ensure its scientific integrity, including patient screening and accrual, follow up, performance of individual centers, data acquisition and quality issues, adverse events, and outcomes. At the first meeting, we will also determine their desire in establishing formalized stopping rules. Any data presented by treatment group at the DSMB meeting will be blinded with regard to the identity of the comparison groups, and participating investigators (except for the study biostatistician) will not see any data broken down by treatment group during the course of the trial.

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Appendix

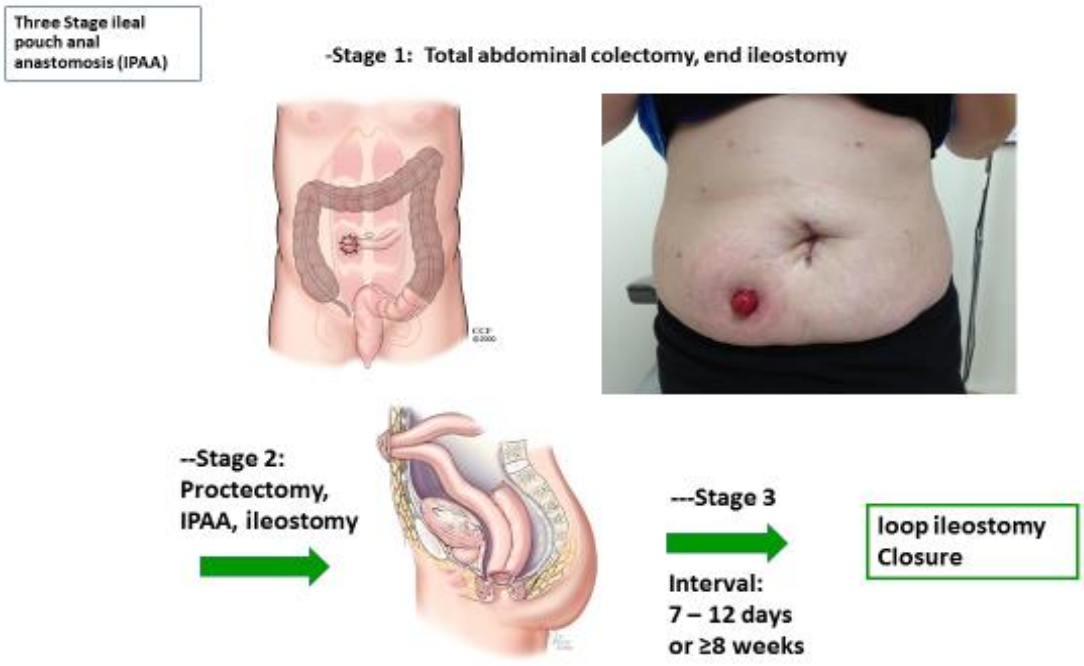
Table: Clavien-Dindo Classification (From Reference #1)

TABLE 1. Classification of Surgical Complications

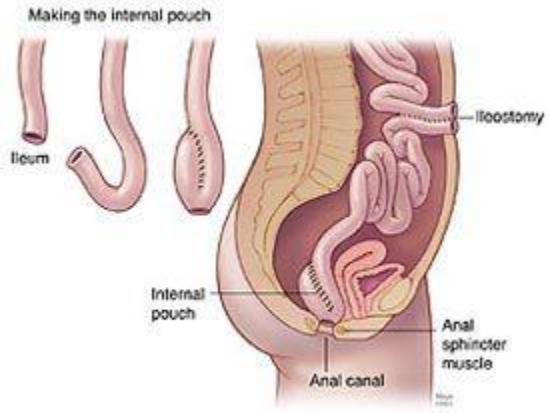
Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. 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 are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

Illustrations:



2-stage IPAA with (loop) ileostomy



Timeline study visits

Procedure	**Timing**	**Location and/or individual responsible**
Inclusion/exclusion criteria assessment	PHASE 1: During IPAA preoperative assessment	Surgical outpatient clinic / Surgeon or trial assistant
Informed Consent #1: obtained from patients who meet initial inclusion and exclusion criteria		
Case Report Form (CRF)-1 completion (Screening)	PHASE 1: During IPAA preoperative assessment	Surgical outpatient clinic / Surgeon or trial assistant
Case Report Form (CRF)-2 completion (Pre-IPAA details)	PHASE 1: Within 2 days of IPAA	REDCap application / Surgeon or trial assistant
IPAA surgery	PHASE 1: At discretion of patient and surgeon and within 30 days of inclusion/exclusion criteria assessment	Study site operating room / surgeon
Case Report Form (CRF)-3 completion (IPAA surgery details)	PHASE 1: Within 2 days of IPAA surgery	REDCap application / surgeon or assistant
Post-IPAA clinical assessment	PHASE 1: Day 5 to 12 after IPAA	Study site inpatient setting / Surgeon
Exclusion of potential study patients judged not clinically suitable for trial entry. Case Report Form (CRF)-4 (IPAA Assessment)	PHASE 1: Day 5 to 12 after IPAA	REDCap application / Study site inpatient setting / Surgeon
Informed Consent #2 – obtained only from potential study patients who are <u>clinically suitable for early ileostomy reversal</u>	PHASE 2: Day 5 to 12 after IPAA, after IPAA <u>clinical</u> assessment	Study site inpatient setting / Surgeon
Radiologic imaging assessment of the IPAA	PHASE 2: Day 5 to 12 days after IPAA	Study site radiology suite
Case Report Form (CRF)-4 completion (IPAA Assessment) - <u>finish</u>	PHASE 2: Day 5 to 12 after IPAA, after IPAA <u>radiological</u> assessment	REDCap application / Study site inpatient setting / Surgeon
Randomization - of study patients who are <u>radiologically suitable for early ileostomy closure</u>	PHASE 2: Day 5 to 12 days after IPAA	Study site trial coordinator office / trial assistant
Ileostomy Closure	PHASE 2: **Experimental Arm:** 7 to 12 days after IPAA surgery **Control Arm**: ≥ 8 weeks after IPAA surgery	Study site operating room

Case Report Form (CRF)-5 completion (ostomy reversal details)	PHASE 2: Within 2 days of ostomy closure	REDCap application / surgeon or assistant
Outcome Assessment #1- Case Report Form (CRF)-6 (complications)	PHASE 2: 0-1 month after randomization.	REDCap application / surgeon or assistant
Outcome Assessment #2- Case Report Form (CRF)-6 (complications)	PHASE 2: 1-2 months after randomization.	REDCap application / surgeon or assistant
Outcome Assessment #3- Case Report Form (CRF)-6 (complications)	PHASE 2: 2-3 months after randomization.	REDCap application / surgeon or assistant
Outcome Assessment #4- Case Report Form (CRF)-6 (complications)	PHASE 2: 3-4 months after randomization.	REDCap application / surgeon or assistant
Outcome Assessment #5- Case Report Form (CRF)-6 (complications)	PHASE 2: 4-5 months after randomization.	REDCap application / surgeon or assistant
Outcome Assessment #6- Case Report Form (CRF)-6 (complications)	PHASE 2: 5-6 months after randomization.	REDCap application / surgeon or assistant
Functional outcome and SF-12 Case Report Form (CRF)-7 completion (Function & SF-12)	PHASE 2: At 6 months after randomization	REDCap application / surgeon or assistant
Case Report Form (CRF)-8 completion (Adverse Events)	PHASE 2: Assessed on a daily interval, during hospitalization(s), after IPAA and ostomy reversal surgery and then reassessed at 1-2 month intervals, until 6 months after IPAA.	REDCap application / surgeon or assistant

Clinical Adverse Event Reporting Form

Short versus long interval to loop ileostomy reversal after ileal pouch surgery in patients with ulcerative colitis (SLIRPS) trial

A randomized, prospective trial investigating the timing of diverting ileostomy closure after ileal j-pouch surgery.

Event ID: _____ Study Center: _____ Study ID: _____

Event Name:_____

DOB: __ __/ __ __/ __ __ __ __ Gender: _____ Race: _____

mm dd yyyy

Name of MD Reporting Event?	_____
Date of Medical Review	__ __/ __ __/ __ __ __ __
	mm dd yyyy
Is this a Serious Adverse Event (SAE)?	☐ Yes ☐ No
Indicate all classifications(s) applicable	☐ Death ☐ Life threatening ☐ Disability ☐ Congenital anomaly/birth defect ☐ Hospitalization - Initial ☐ Hospitalization - Prolongation ☐ Other
Specify Other	
Relationship/Causality (likelihood that study agent caused the event)	☐ Not related ☐ Probably not related ☐ Possibly related ☐ Related

	Is the event Expected? Is the event Unexpected?

MD Narrative:	
Measures at the onset of adverse event	☐ None ☐ Surgical Procedure ☐ Treatment with medication ☐ Other
Specify Other:	
Outcome of event (sequelae are defined as conditions following and resulting from event)	☐ Recovered without sequelae ☐ Recovered with sequelae ☐ Not yet recovered ☐ Died
Signature of Study Center MD	_____
Date Form Completed	__ __/ __ __/ __ __ __ __ mm dd yyyy

Lead Study Principal Investigator assessment:

Soes this event suggests that the research places subjects or others at greater risk of physical of psychological harm than was previously known or recognized?

❑Yes ❑No

Within 5 days of knowledge of event please email:

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