Randomized Trial of Prolonged Use of Negative Pressure Wound Therapy in Patients Undergoing Surgical Procedures for the Management of Gastrointestinal Malignancies

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ROLE OF MULTIPLE PRINCIPAL INVESTIGATORS

DR. PIMIENTO: is an Associate Member in the Department of Gastrointestinal Oncology. Dr. Pimiento will serve as the primary PI of the study and will be overseeing the day-to-day activities, including eligibility, randomization and clinical data collection.

DR. ANAYA: is a Senior Member in the Department of Gastrointestinal Oncology and will assist Dr. Pimiento as the Co-PI of proposed study.

Both PI and Co-I will direct the care and surgery of the patients.

PROJECT SUMMARY

Background/Rationale: Postoperative surgical site infections (SSIs) are one of the most frequent surgical complications and a major cause of postoperative morbidity, prolonged hospital stay, health care costs and mortality. Patients with cancer who are undergoing surgical procedures have an increased risk of SSIs. Negative pressure wound therapy (NPWT) dressings have been used on primarily closed incisions to reduce surgical site infections in other surgical disciplines. However, there is limited clinical evidence examining the use of NPWT to reduce SSIs in high-risk cancer patients undergoing curative-intent surgical resection.

Objectives: This study proposes to estimate the effectiveness of prolonged use (7 days) of NPWT in an oncologic setting. We plan to address the following aims: 1) To estimate the effectiveness rate of the NPWT dressing in decreasing wound infection for oncologic gastrointestinal surgical procedures; 2) To evaluate if usage of NPWT is associated with earlier return to intended oncologic therapy (RIOT) after surgical resections for gastrointestinal cancer; and 3) To test the difference in SSI between standard wound therapy versus NPWT in decreasing wound events after oncologic gastrointestinal procedure. We hypothesize use of the negative pressure dressing could decrease the incidence of postoperative infection complication (SSI) and possibly lead to faster initiation of antineoplastic therapy.

Methods: We plan to conduct a phase II/III single-center, randomized, controlled trial to evaluate surgical incision closure using NPWT in patients with gastrointestinal neoplasms for which surgical resection are planned, as part of curative-intent treatment. Enrolled patients will be stratified based on the surgery type/location, and then randomly assigned to receive either NPWT or a standard wound closure using a 2:1 block randomization strategy. The primary outcome measure will be the rate of surgical site infections within 30 days postoperatively, defined according to criteria of the US Centers for Disease Control and Prevention. Secondary outcomes include return to intended oncologic therapy (RIOT) and time to RIOT.

A. SIGNIFICANCE

A.1 Epidemiology of Surgical Site Infections: It is estimated that over 40 million surgical procedures are performed every year in the United States. Surgical site infections (SSIs) complicate approximately 2–5% of these procedures,[1] with the highest rates occurring after abdominal surgery.[2] Patients undergoing gastrointestinal and hepatopancreatobiliary (HPB) surgery are reported to have increased SSI rates ranging from 8% to 25%.[3] SSIs are the seconding leading cause of nosocomial infections overall, and the first cause of nosocomial infections for surgical patients, occurring at a rate of 38%.

A.2 Impact of SSI on Morbidity, Mortality & Health Care Costs: While advances have been made in infection control practices, including improved operating room ventilation, sterilization methods, barriers, surgical technique, and availability of antimicrobial prophylaxis, SSIs remain a leading source of morbidity, mortality, prolonged hospitalization and increased health care costs. Multiple patient co-morbidities and risk factors, in addition to procedure-related risk factors, can impact the risk of SSI.[4] Risk factors include diabetes, smoking, immunosuppression, malnutrition, wound class, and operative time (vs. median surgical time). Patients with SSI are more prone to develop additional complications, including wound dehiscence, hernias, and complicated infections such as necrotizing soft tissue infections. Multiple large, single-center, multicenter, and population-level analyses have revealed at least a two-fold increased risk of postoperative mortality in patients with SSI.[5,6] SSI is associated with a mortality rate of 3%,[5,7] and 75% of SSI associated deaths are directly attributable to the SSI.[8] Additionally, compared to controls, SSI is associated with longer hospital stays (10 to12 excess days), a higher risk of intensive care unit (ICU) admission, and a five-fold higher risk of hospital readmission.[5] Furthermore, SSIs represent a significant financial burden to the health care system. Direct and indirect costs from SSIs include increased hospital length of stay, readmissions for treatment including repeat surgical procedures, outpatient and emergency care visits, use of ancillary services, additional medications (including prolonged antimicrobial therapy), lost productivity, and temporary or permanent disability.[9] Estimated average attributable costs of SSIs range from $10,443 to $25,546 per infection,[10,11] resulting in $3.5-$10 billion in annual direct health care costs.[12] It is estimated that 55% of SSIs are deemed preventable by application of evidence-based strategies.[13,14]

A.3 SSI in Cancer Patients: Patients with cancer who are undergoing surgical procedures have an increased risk of SSIs.[15] Although mortality has improved for patients undergoing major abdominal surgery for gastrointestinal,[16] pancreatic,[17] and peritoneal surface[18] malignancies, morbidity is still significant and can affect up to 50% of patients.[19] Incidence of SSI varies depending on surgical procedure, with the highest incidence associated with liver resection with 22-26%, following pancreas resection (21%), esophageal resection (15-20%) and gastric resection (15%). Infectious complications in cancer patients having surgery are also associated with decrease survival and overall worse long-term outcomes;[20] this is thought to be due to the inflammatory response, as well as the impact postoperative complications may have on initiation/completion of adjuvant therapies.[21] Given this paradigm, infectious complications related to the gastrointestinal procedure could possibly prevent patients from Return to Intended Oncologic Treatment (RIOT) and negate some or all of the benefits of surgery.[21]

B. INNOVATION: NEGATIVE PRESSURE WOUND THERAPY

Risk factors for SSI may occur at multiple points during the pre-operative, operative and post-operative phases. Efforts to reduce SSI often include a limited number of selected interventions that are grouped together in a "care bundle",[3] but compliance with a care bundle is not assured.[22] ***Negative pressure wound therapy (NPWT) is emerging as a promising technology as a preventative intervention***. NPWT has traditionally been used for complex open wounds in both acute and chronic setting. NPWT has revolutionized the treatment of complex wounds. The negative pressure has been shown to reduce the lateral stresses on surgical closures by nearly 50% at the level of the epidermis, dermis, and within the subcutaneous tissues.[23] This stabilizing effect on the closed incision keeps superficial and deeper tissue layers in contact with one another without shearing. The direction of tissue stresses more closely resembles intact tissues by bolstering the surgical closure in both the horizontal axis and vertical axis. Sealing of the incision from outside contamination through maintenance of a closed and sterile environment is an obvious function of NPWT. In

addition, there are potential theoretical benefits of fluid removal, stimulation of cell proliferation through macro- and micro-deformation of tissue, reduction of inflammatory mediators, and increasing tissue oxygen tension.[24,25]

There is growing clinical evidence suggesting, when compared to standard surgical dressing, NPWT can substantially reduce wound complications and SSIs in closed primary incisions[25-29], and specifically, closed abdominal laparotomy incisions in general surgery patients.[30-32] However, there is limited clinical evidence examining the use of NPWT to reduce SSIs in high-risk cancer patients undergoing surgery.

C. PURPOSE AND OBJECTIVES

The objective of this study is to evaluate the effectiveness of prolonged use (7 days) of the negative pressure dressing NPWT in an oncologic setting. We hypothesize that use of the negative pressure dressing could decrease the incidence of postoperative infection complication (SSI) and possibly lead to faster initiation of antineoplastic therapy. Therefore, we propose to conduct a phase II/III single-center, randomized, controlled trial to address the following aims:

> ***Specific Aim 1:*** To estimate the effectiveness rate of the extended (7 days) use of a NPWT dressing in decreasing wound infection for oncologic gastrointestinal surgical procedures
>
> ***Specific Aim 2:*** To evaluate if usage of NPWT is associated with earlier return to intended oncologic therapy (RIOT) after surgical resections for gastrointestinal cancer
>
> **Specific Aim 3:** To test the difference in SSI between standard wound therapy versus NPWT in decreasing wound events after oncologic gastrointestinal procedure

D. PRELIMINARY EVIDENCE

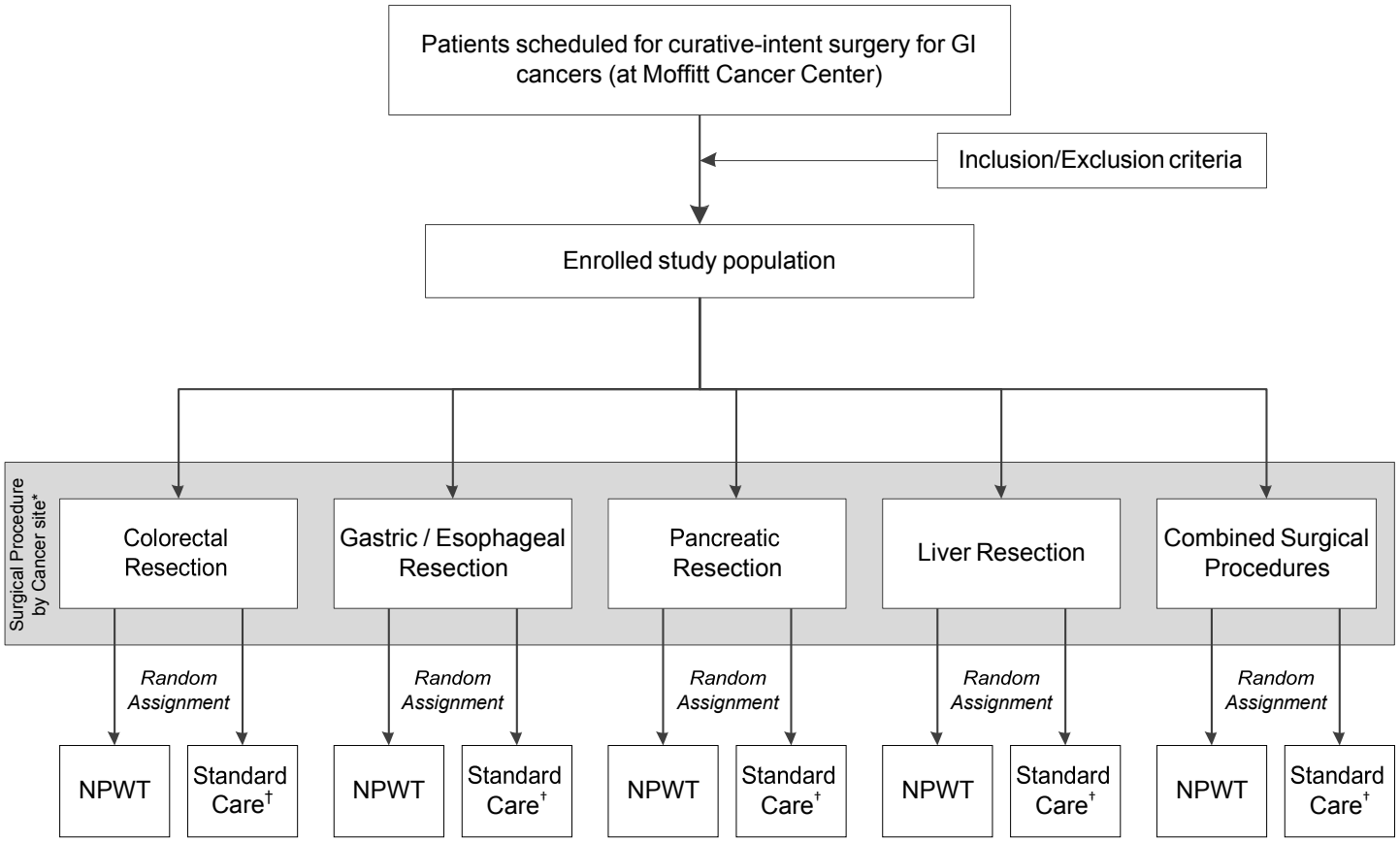
D.1 Identifying cancer patients at increased risk of surgical site infection[33]: We conducted a prospective cohort of 503 cancer patients undergoing elective operations at a tertiary cancer center sought to 1) identify cancer-specific predictors of postoperative SSI; 2) develop a risk-stratification prognostic tool; and 3) compare its performance with traditional measures. SSIs were found to be common among cancer patients with a 30-day incidence of 24%. Significant predictors of SSI included preoperative chemotherapy (OR 1.94 [95% CI, 1.16-3.25]), clean-contaminated wounds (OR 2.1 [95% CI, 1.24-3.55]), operative time ≥2 hours (OR 1.75 [95% CI, 1.01-3.04]) and ≥4 hours (OR 2.24 [95% CI, 1.22-4.1]), and surgical site: groin (OR 4.65 [95% CI, 1.69-12.83]), and head/neck (OR = 0.12 [95% CI, 0.02-0.89]). A Risk of Surgical Site Infection in Cancer (RSSIC) score was developed/validated and improved risk-stratification of cancer patients by identifying those that may benefit from more aggressive or novel preventive strategies.

D2. Incidence and impact of postoperative infections on cancer patients – long term outcomes[20]: We conducted a retrospective cohort study to characterize the effect of postoperative complications on long-term survival on 12,075 patients undergoing resection for non-metastatic colorectal cancer (CRC) from 1999 to 2009. We analyzed a merged national dataset of the Veterans Affairs Surgical Quality Improvement Program and Central Cancer Registry, and found that overall morbidity and infectious complication rates were 27.8% and 22.5%, respectively. The presence of any complication was independently associated with decreased long-term survival (hazard ratio [HR], 1.24; 95% confidence interval [1.15-1.34]). Multivariate analysis by complication type demonstrated increased risk only with infectious complications (HR, 1.31; 95% confidence interval [1.21-1.42]). Subset analysis demonstrated this effect predominantly in patients with severe infections (HR, 1.41; 95% confidence interval [1.15-1.73]). Our findings suggest the presence of postoperative complications after CRC resection is associated with 1) decreased long-term survival, 2) independent of patient, 3) disease, and 4) treatment factors. Most importantly, the impact on long-term outcome is primarily driven by infectious complications, particularly severe postoperative infections.

E. APPROACH

E.1 Study Design: We propose to conduct a phase II/III single-center, randomized, controlled trial evaluating surgical incision closure using NPWT in patients undergoing surgical procedures as part of the treatment for active cancer, and including: colorectal resections, esophagectomy, gastrectomy, pancreatic resection, liver resections, and combined operations. Patients will be stratified based on the surgical procedure (as described) and type (minimally invasive [laparoscopic, hand-assisted, and robotic] versus open). Patients will then be randomly assigned to receive either NPWT or a standard wound closure using a 2:1 randomization strategy (**Figure 1**). Demographic, operative and outcomes data will be prospectively collected.

Figure 1. Study Flowchart



*All surgical cases will be stratified based on minimally invasive vs. open approach

†Standard wound care includes the following: 1) Dermabond as sole coverage for the wound, 2) sterile dressing and tape and 3) occlusive sterile dressing.

Where GI = gastrointestinal, NPWT = Negative pressure wound therapy

E.2 Study Site: The study will be conducted at Moffitt Cancer Center.

E.3 Study Population: The proposed study will focus on patients with gastrointestinal neoplasms for which surgical resection are planned, as part of curative-intent treatment. All patients will be consented, screened and enrolled once surgery is scheduled.

E.3.1 Inclusion criteria: To be eligible to participate in the study, an individual must meet all of the following criteria:

1. Male or female aged ≥18 years
2. Scheduled surgical procedure for the management of gastrointestinal cancer (as shown in **Figure 1**)
3. Scheduled surgical procedure planned for incision that will result in wound > 5cm
4. Scheduled surgical procedure planned for skin wound that will be closed by primary intention with either:
    a. Staples covered by sterile Telfa® and Tegaderm® or Medipore®

b. Dermal or subcuticular sutures covered by Octil®

5. Provision of signed and dated informed consent form
6. Stated willingness to comply with all study procedures and availability for the duration of the study

E.3.2 Exclusion criteria: An individual who does not meet inclusion criteria and meets any of the following criteria will be excluded from participation in this study:

1. Scheduled surgical procedure where wound will be considered dirty
2. Scheduled surgical procedure for wound left for closure by secondary intention
3. Emergency surgery
4. Pregnancy status is confirmed per Moffitt Protocol the day of surgery in the preoperative space by urine pregnancy test in patient younger than 65 and with intact uterus. Pregnant patient will be excluded from this study
5. History or current diagnosis of any medical or psychological condition that in the Investigator's opinion, might interfere with the subject's ability to participate in the study or the inability to obtain informed consent because of psychiatric or complicating medical problems

Participant will be excluded from analyses if the planned surgical procedure is not performed.

E.4 Recruitment Procedures: The project coordinator will use a structured protocol to identify potential participants and enroll target samples of patients. Eligible patients will be enrolled from the Gastrointestinal Clinics at the Moffitt Cancer Center to achieve targeted recruitment goals. As part of standard care, all patients with gastrointestinal neoplasms are first discussed in weekly multidisciplinary tumor boards where treatment recommendations are given surgeons, medical oncologists, interventional radiologists, radiation oncologists, pathologists, radiologists and ancillary services. When candidates are considered for surgical resection, patients are then seen in the clinic and after a thorough evaluation may be offered curative-intent surgery for management of their cancer, as deemed appropriate by the GI surgical oncologist. To maximize recruitment strategy, a waiver of HIPAA authorization (see **Section H.3.1**) will be obtained to identify potential subjects from clinic lists (i.e., screening procedures), located within the electronic medical records (EMR). During the initial visit, inclusion and exclusion criteria will be verified by PIs and clinical trial coordinator. Prior to performing any study specific procedure, a signed consent form will be obtained for each subject. Details regarding consent procedures are described in **Section H.3**.

E.5 Randomization & Blinding Arrangements: Randomization will occur on **Visit 2**. Given the appearance of dressings are dissimilar, it is impossible to blind surgical oncologists and subjects through the study period. However, surgical oncologists (including investigators) will be blinded of treatment randomization until the dressing is applied to the wound. We will utilize a block randomization strategy that will randomly assign patients to receive either NPWT or a standard wound closure, in a 2:1 ratio (**Figure 1**). A web-based program, Clinical Trials Subject Registration & Randomization (SRAR), will be used to randomly assign subjects to arms of the study. Unique to this application is the ability to programmatically determine eligibility and randomize the individual to the appropriate stratum.[34] The random allocation sequence will be generated by the biostatistician (co-investigator: Dr. Schell), who will remain unblinded throughout the study. On the day of the surgical procedure (Visit 2) and up to 3 days before, the subject will be randomized to the next sequential arm in the selected strata, and an email will be generated to notify unblinded members of the research team. The assigned study arm will not be available to the surgical oncologists until treatment allocation is revealed.

E.5.1 Concealed treatment allocation: Treatment allocation will be concealed from the surgical oncologist performing the resection until the end of the surgical procedure, before dressing the wound. After randomization, an unblinded member of the research team will receive an email from SRAR regarding the subject's treatment allocation. This individual will contact the subject's operating room and share treatment allocation. When the wound is ready to be dressed, the surgical oncologist will be advised of the arm the subject has been assigned to and apply the appropriate dressing.

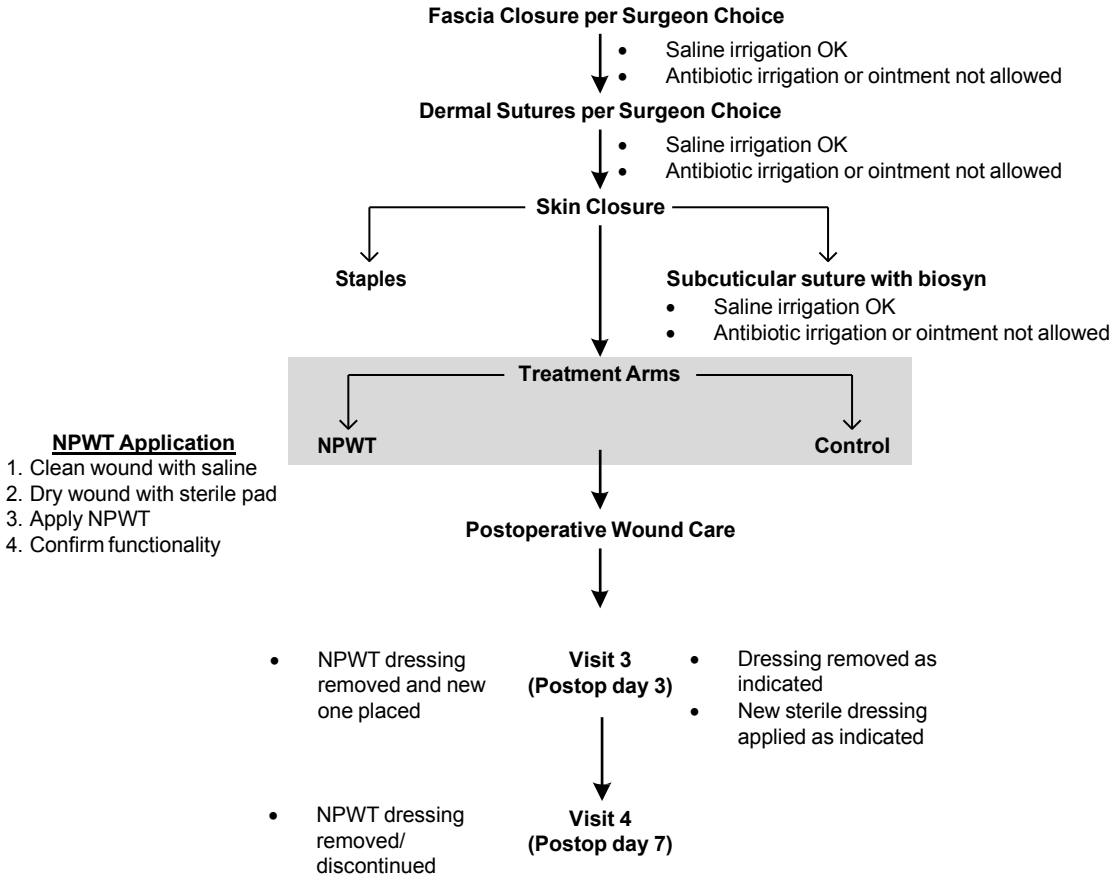
E.5.2 Treatment arm - NWPT: Wound management procedures after surgical procedures for both treatment arms are shown in **Figure 2**. Patients randomized to NPWT will receive the PICO (Smith & Nephew), a single-use NPWT that produces continuous negative pressure at -80 mmHg. Randomized patients will have their fascia and skin closed in the same manner as the control arm patients (**Figure 2**). NPWT will be applied after

the surgical site is completely cleaned and dry. NPWT dressing will be removed and replaced during **Visit 3**, and removed/discontinued on **Visit 4.**

E.5.2.1 Treatment arm failed NPWT: If NPWT dressing malfunctioned and the seal is lost, the subject will receive Telfa® covered with Tegaderm® or Medipore® (standard wound dressing) and recorded as dressing failure.

E.5.3 Control arm - Standard wound dressing: Patients randomized to the control arm (standard wound dressing) will be closed in the standard fashion (**Figure 2**). Standard wound dressing will be covered under sterile conditions utilizing the one of the following, per the operating surgeon's discretion/preference: 1) Staples covered with sterile Telfa® covered with Tegaderm® or Medipore®, or 2) Dermal or subcuticular sutures covered with Octil®.

Figure 2. Wound Management: Treatment and Control Arms



E.6 Study Visits: Study visits and activities are listed in **Table 1**. To maximize subject retention and minimize burden to patients and the clinic flow, study visits are aligned with appointments and clinical care of patients with gastrointestinal neoplasms at Moffitt Cancer Center and include activities performed during routine clinical care.

Table 1. Study Activities Corresponding to Study Visits

Activity	STUDY VISITS						
	Visit 1	**Visit 2**	**Visit 3 POD 3**	**Visit 4 Discharge Date**	**Visit 5 POD 10-15**	**Visit 6 POD 30-45**	**Visit 7 POD 60-90**
	Initial visit	*Surgical Procedure*	*Postoperative Assessments*				*Final Visit*
Inclusion/exclusion criteria confirmed	X						
Informed consent	X						
Medical history review	X	X			X	X	X
Physical examination	X	X	X		X		
Vital signs	X	X	X		X		
ECOG performance status	X				X		
Blood draw results	X	X					
Surgical resection		X					
Randomization		X					
Concomitant medication review	X	X	X	X	X	X	X
Adverse events review			X	X	X	X	X
Surgical site review			X*	X*	X	X	X
Telephone assessment						X	X

*Discharge can occur during this time period. When participant is discharged, dressing will be removed and data regarding surgical site will be recorded. If participant is discharged before study visit, then data will be collected via short telephone interview.
†Details listed in text of Methods section
Where POD=post-operative day, ECOG=European Cooperative Oncology Group performance status (a scale to assess how a patient's disease is progressing)

E.6.1 Initial visit: The initial visit will align with patient's clinic visit with surgical oncologist prior to surgical procedure. After obtaining informed consent for the study, the following procedures and assessments will be completed during the first study visit:

- Confirm inclusion/exclusion criteria
- Informed consent
- Complete review of medical and surgical history, including history of malignancy
- Routine physical examination including height and weight, HEENT, lymph nodes, cardiopulmonary and musculoskeletal systems, abdomen and extremities (part of routine clinical care – performed by surgical oncologist)
- Vital signs including blood pressure, heart rate, respiratory rate, temperature (routine clinical care)
- ECOG performance status
- Review CT scan, obtained for routine clinical care (to determine eligibility)
- Blood draw results, obtained for routine clinical care (may review results obtain up to 2 weeks prior to consenting):
    - Complete blood count (CBC) + / - differential (based on PI's or treating physician's discretion) and platelet count
    - Clinical chemistry panel: Glucose, calcium, albumin, total protein, sodium, potassium, CO2 , chloride, BUN, creatinine, alkaline phosphatase (ALP), ALT, AST and bilirubin
- Concomitant medication review

E.6.2 Visit 2 (Day of Scheduled Surgery): All participants will undergo surgical resection for curative intent and will be ***randomized to receive either NPWT or a standard wound closure, in a 2:1 ratio***. Randomization may occur up to 3 days prior to surgery date.

Prior to Surgery/Randomization:

- Review of medical history
- Routine physical examination
- Vital signs
- Blood draw results, obtained for routine clinical care (can be obtain before or after surgical procedure):
    - Complete blood count (CBC) +/- differential (based on PI's or treating physician's discretion) and platelet count
    - Clinical chemistry panel: Glucose, calcium, albumin, total protein, sodium, potassium, CO2 , chloride, BUN, creatinine, alkaline phosphatase (ALP), ALT, AST and bilirubin
- Concomitant medication review

E.6.3 Visit 3: The third visit will occur while the subject is in the hospital, 3 days after the surgical procedure. During this time, subjects will undergo the following assessments:

- Routine physical examination
- Vital signs
- Concomitant medication review
- Adverse events review
- Surgical site review: Surgical incision (per guidelines outlined **Table 2**) and surgical dressing will be assessed (see **Section E.8.1**). Integrity of dressing and any soilage of the gauze will be noted.

E.6.4 Visit 4 (Discharge Date): The fourth visit will occur on the date of hospital discharge after surgery date. The dressing will be removed and data regarding surgical site will be recorded. The following will be performed:

- Concomitant medication review
- Adverse events review
- Surgical site review

E.6.5 Visit 5: The following assessments will be performed during the patient's routine outpatient follow-up visit with the surgical oncologist (for wound care) 10-15 days after hospital discharge. Routine follow-up visit may be in-person or virtual visit:

- Medical history review
- Physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, temperature)
- ECOG performance status
- Concomitant medication review
- Adverse events review
- Surgical site review

E.6.6 Visit 6: The patient will be contacted by a research coordinator via telephone 30-45 days post-discharge date. Similar to **Visit 4**, the research coordinator will follow a structured

Table 2. Primary Outcome Criteria: SSI Definition

SSI Classification	Definition
Superficial Incisional	1. Occurs within 30 days after the operation, and 2. Involves only skin or subcutaneous tissue of the incision, and 3. At least one of items A to D A. Purulent drainage from the superficial incision B. Organism isolated from an aseptically obtained culture of fluid or tissue from the superficial incision C. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and incision is deliberately opened by surgeon and is culture-positive or not cultured D. Diagnosis of superficial incisional SSI by the surgeon or attending physician
Deep Incisional*	1. Occurs within 30 days after the operation, and 2. Involves deep soft tissues of the incision, and 3. At least one of items A to D A. Purulent drainage from the deep incision but not from the organ/space component B. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38 °C), localized pain, or tenderness, unless site is culture-negative C. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiological examination D. Diagnosis of superficial incisional SSI by the surgeon or attending physician
Organ/Space	1. Occurs within 30 after the operation, and 2. Involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation, and 3. At least one of items A to D A. Purulent drainage from a drain that is placed through a stab wound into the organ/space B. Organisms isolated from an aseptically obtained culture of fluid or tissue C. An abscess or other evidence of infection found on direct examination, during reoperation, or by histopathologic or radiologic examination D. Diagnosis of superficial incisional SSI by the surgeon or attending physician

Adopted from Chiu, Dellinger and Anaya 2017[6]
*Infection that involves both superficial and deep incision sites will be reported as deep incisional SSI; organ or space SSI that drains through the incision as deep incisional SSI[14,35]

telephone guide to assess whether the patient had any problems with the surgical incision or received any incisional care at another facility. The telephone interview will ensure that all patients have a 30-day follow-up to capture any surgical site complications that occurred after surgery and might have been diagnosed and treated at another facility. In addition to the short telephone interview, the research coordinator will also conduct an EMR review. The following will be performed during **Visit 6**:

- Medical history review
- Concomitant medication review
- Adverse events review
- Surgical site review: The patient will be asked if there are any problems with the surgical incision or received any incisional care at another facility. The surgical site will be evaluated by surgical staff via telemedicine or in person if concerns are reported to research staff during this visit.

E.6.7 Final Visit: The final visit will occur 60-90 days after discharge date. Using the same structure as **Visit 6**, the research coordinator will contact the patient and conduct EMR review for the following assessments:

- Medical history review
- Concomitant medication review
- Adverse events review
- Surgical site review: The patient will be asked if there are any problems with the surgical incision or received any incisional care at another facility.
- RIOT (secondary outcomes – see **Section E.7.2**)
- Time to initiation of planned oncologic therapy (secondary outcomes – see **Section E.7.2**)

E.7 OUTCOMES

E.7.1 Primary Outcome

The primary outcome of interest is superficial, deep wound or organ/space SSIs within the initial 30-day postoperative period. SSI definitions (**Table 2**) are based on the American College of Surgeons' National Surgical Quality Improvement Program (NSQIP) and Centers for Disease Control and Prevention (CDC).[14] Surgical incisions will be assessed by a member of the research team at all postoperative study visits (inpatient and outpatient). Any signs of infection, as defined by **Table 2**, will be noted accordingly. If a surgical site complication is diagnosed or suspected by the primary surgical team, a member of the study will be called in to assess the incision. SSI will be treated per guidelines of routine medical care at Moffitt Cancer Center.

i. **Superficial Incisional SSI**: Superficial incisional SSI involves only skin or subcutaneous tissue of the incision within 30 days after surgical procedure and at least one of the following:

a) Purulent drainage, with or without laboratory confirmation, from the superficial incision,
b) Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision,
c) At least one of the following signs or symptoms of infection: i) pain or tenderness, ii) localized swelling, redness, or heat AND superficial incision is deliberately opened by the surgeon, unless incision is culture-negative, and/or
d) Diagnosis of superficial incisional SSI by the surgeon or attending physician

ii. **Deep Incisional SSI**: Deep Incision SSI is an infection (within 30 days of operation) that appears to be related to the operation and infection involves deep soft tissues (for example, fascial and muscle layers) of the incision and at least one of the following:

a) Purulent drainage from the deep incision but not from the organ/space component of the surgical site
b) A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (> 38 C), localized pain, or tenderness, unless site is culture-negative
c) An abscess or other evidence of infection involving the deep incision is found on direct examination, during re-operation, or by histopathologic or radiologic examination
d) Diagnosis of a deep incision SSI by a surgeon or attending physician

iii. **Organ/Space SSI**: Organ/Space SSI appears to be related to the operation (within 30 days of surgery) and the infection involves any part of the anatomy (for example, organs or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following:

a) Purulent drainage from a drain that is placed through a stab wound into the organ/space.
b) Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space

c) An abscess or other evidence of infection involving the organ/space that is found on direct examination, during re-operation, or by histopathologic or radiologic examination
d) Diagnosis of superficial incisional SSI by the surgeon or attending physician

E.7.2 Secondary Outcomes: Secondary outcomes include:

i. RIOT: Postoperative electronic medical oncology records of all enrolled participants will be reviewed to separate patients into two groups: a) those who could return to intended oncologic therapy and b) those who could not. The exact reason(s) for failure to RIOT will be documented, including postoperative complications or poor general performance status.

ii. Time to initiation of planned oncologic therapy: Time to initiation planned therapy will be recorded from the surgery date to initiation date of planned oncologic therapy.

E.8 Statistical Analyses

E.8.1 Sample Size: Our plan is to enroll 200 patients on the NPWT arm and 100 to the standard-of-care arm in a randomized trial. Patients will be in 10 groups, based on surgical procedure/cancer type and type of surgery (laparoscopic vs. open approach). The approximate counts anticipated are: colorectal resections (N=100), gastroesophageal resections (N=50), pancreatic resections (N=50), liver resections (N=80), or a combination of them (N=20). The anticipated counts for type of surgery are: open (N=270), laparoscopic (N=30). Block randomization will be employed to ensure the accrual to the two arms is balanced. The laparoscopic-disease subgroups will be fairly small, but blocking will still be of value here.

E.8.2 Analytic Approach: Given our study objectives and aims, we intend to analyze data as intention-to-treat.

i. Demographic and Other Baseline Characteristics: Standard baseline demographic (age, race, ethnicity, etc.), clinical and tumor-related characteristics, including preoperative treatment regimen (chemotherapy and radiation), nutritional status, preoperative albumin level, usage of bowel prep (when indicated) and wound protector usage will be analyzed using descriptive statistics.

ii. SSI benchmark (Specific Aim #1): For the two arms, we will obtain 90% confidence intervals. For the NPWT arm, **Table 3** shows the 90% upper confidence limits (UCLs) for the SSI rate for theoretical rates, ranging from 5% to 12%, for a sample of size 200. Note that the UCLs are 3-4% higher.

Table 3. 90% Upper Confidence Limits for a Given Wound Rate (N=200)								
SSI Rate	.05	.06	.07	.08	.09	.10	.11	.12
Upper Confidence Limit	.082	.094	.106	.117	.129	.140	.152	.163

For the standard-of-care arm, we anticipate a higher SSI rate. In **Table 4**, we show the 90% lower confidence limits (LCLs) for the SSI rate for theoretical rates, ranging from 18% to 25%, for a sample of size 100. Note that the LCLs are 5-6% lower.

Table 4. 90% Lower Confidence Limits for a Given Wound Rate (N=100)								
SSI Rate	.18	.19	.20	.21	.22	.23	.24	.25
Lower Confidence Limit	.126	.134	.143	.151	.160	.168	.177	.186

Our primary aim is to obtain these two confidence intervals. We employ a 2:1 randomization plan, as we are most interested in estimating the SSI rate for NPWT. We will also obtain estimates for each of the disease subgroups. Notably, the 90% CIs will be larger due to smaller samples sizes.

iii. RIOT comparison (Specific Aim #2): We will use the log-rank test to test if NPWT is associated with earlier RIOT after surgical resections. Overall, we expect that about 75% will be RIOT-eligible in each arm (requiring additional therapy). Assuming that at 12 months 75% and 60% will RIOT in the standard-of-care and NPWT arms, respectively, we will have 41% power, given patient accrual occurs over 12 months and total follow-up time is 12 months. If the follow-up time is extended to 18 or 24 months, the power increases to 67% and 85%, respectively.

iv. Comparing NPWT vs standard of care for the primary outcome (Specific Aim #3): We will formally test for a statistical difference in the SSI rates in the two arms. This will be done using a 2-sided unconditional test, with $\alpha = 0.05$. Let SSI1 and SSI2 be the true proportion of SSI rates in the better and inferior arms. We will have +80% power under the following situations: If SSI2 = 0.18 - 0.19, then SSI1 ≤ 0.07; SSI2 = 0.20, then SSI1 ≤ 0.08; SSI2 = 0.21 - 0.22, SSI1 ≤ 0.09; SSI2 = 0.23, SSI1 ≤ 0.10, SSI2 = 0.24, SSI1 ≤ 0.11; and SSI2 = 0.25, SSI1 ≤ 0.12. From these results, we will reject if the difference is in the 11-13% range. We will also test for SSI

rate differences among the 4 disease subgroups (excluding the combination subgroup) using a 2x4 chi-square test. This test will have low power, but may yield a statistically significant finding.

F. FUTURE DIRECTIONS

Findings from our proposed study are critical for the development of practice changing guidelines for the management of wounds in gastrointestinal oncologic procedures. Data will lay the groundwork for subsequent studies in the impact of wound complications and delay of return to indeed oncologic therapy and allow us to limit the impact of this complication in oncologic outcomes, while establishing means to implement changes in a standardized fashion.

G. TIMELINE/STUDY DURATION

The project timeline is depicted in the GANTT chart. The study will be determined complete when all enrolled patients have discontinued from the study and study objectives have been evaluated.

GANTT Chart: Timeline of Research Plan

TASKS	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Start-up procedures*												
Patient enrollment (N=300)												
Data analyses												
Abstract/manuscript preparation												
Extramural grant preparation												

*Start-up will include SRC/IRB approval, SOP, case report forms and database development; SRC/IRB protocol will be submitted prior to Month 1 (July 2019).

H. PROTECTIONS FOR HUMAN SUBJECTS

H.1 Potential Risks and Discomforts

H.1.1 Procedures to Maintain Confidentiality: There is a potential risk for the loss of confidentiality for all study participants; however, every precaution will be taken to ensure all PHI and data collected as part of the study is kept confidential. The risk for loss of confidentiality will be minimized by the following procedures. Identifiers will be removed at the earliest opportunity. Identifiable information (name, MRN) will be used only during data collection from medical chart reviews, after which a unique numerical identifier (i.e., study ID) will be assigned to each patient and the identifiable information will no longer be used or included in the main database. The study ID will link data collected directly from participants and from electronic medical reviews. Collected data will be entered and maintained in OnCore and Moffitt's electronic Clinical Trials Management System. Details regarding Data Management are in **Section 6**. Only the research team will have access (as deemed by the PI) to the completed dataset and other study files. Files will be password-protected.

All direct identifiers (e.g., patient's medical record number, date of birth, etc.) will be destroyed once all data collection and analysis for the study has been completed. Patients' de-identified data will be kept be stored in a password-protected computer database or locked office at Moffitt Cancer Center, per the policy and requirements (for a period of five years from the date the IRB accepts the final report submitted by the PI). The PI will keep a subject enrollment log showing study ID, names and addresses. All documents will be stored in strict confidence. Only members of the research team will have access to the data collected as part of this study. All reports generated as a result of the analysis will be without identifiers.

H.1.2 Risks Associated with NPWT: There is no reported increased incidence of wound complications with the use of the NPWT dressing. No additional risks for study participants are anticipated, since the safety and feasibility of the application of NPWT on postoperative wounds has been established in several previous studies.[36]

H.1.3 Risks Associated with Study Procedures – Gastrointestinal Resection: Patients enrolled in the study will have surgical resection of gastrointestinal structures as part of the standard management of

gastrointestinal malignancies. Although this procedure is not study-related specifically, it may have adverse events/complications that can alter the progress of the patients and the study. The occurrence of any of these known postoperative complications will be recorded, tracked and evaluated by an experienced clinical team as part of routine care and to identify any potential study-related adverse events.

The gastrointestinal resection will be performed as part of routine care for the treatment of gastrointestinal neoplasms and does not represent a procedure specific to the study. There is a risk of medical and surgical complications that can occur with any procedure or with administration of anesthesia, including but not limited to:

Medical complications:

- Respiratory failure
- Pneumonia
- Cardiac arrest
- Myocardial infarction
- Venous thromboembolism (Deep venous thrombosis/Pulmonary embolism)
- Arrythmia
- Stroke

Surgical complications – related to gastrointestinal resection:

- Infection
- Anastomotic complications
- Bleeding/hematoma
- Injury to surrounding structures, tissues/organs
- Need for reoperation
- Sepsis
- Liver failure
- Bile leak
- Biloma
- Wound dehiscence
- Allergic reactions
- Separation of the wound
- Blood vessel and/or nerve injury
- Worsening and/or recurrence of symptoms affected by the surgical procedure
- Brain, spine or other nervous system damage
- Chronic pain
- Death

H.2 Benefits

The proposed study will evaluate the impact of NPWT on the risk of SSI and other post-operative outcomes among cancer patients undergoing surgery. There is a possibility this study (i.e., use of NPWT) could provide immediate benefit to individual study subjects. This study may provide more data and a better understanding of utilizing a single-use NPWT to reduce the risk of SSI in a cancer population. The findings from the propose study may provide a foundation to explore other surgical procedures where NPWT may optimize patient outcomes. Given the potential risks and benefits associated with this study, we believe the anticipated benefits outweigh the potential risks; thus, risk-benefit ratio is favorable.

H.3 Consent Procedures

Participants will be identified for inclusion in this study by review clinic lists (see **Section H.3.1**) and clinic leaders of the Gastrointestinal Oncology Service. During Visit 1, upon confirmation of surgical candidacy and treatment plan established (i.e., surgery scheduled), eligible patients will be approached by a member of the research team to conduct consent procedures. The subject will be given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The team member will note that participation is voluntary, and that a decision to not participate will in no way negatively impacts clinical care.

Subjects will also be notified that they are free to discontinue from the study at any time and will be allowed time to consider the information provided. Informed consents will be signed by all participants before any study-specific procedures are performed. In addition, the institution's surgical consent form for invasive procedures will be signed prior to surgery.

H.3.1 Waiver of HIPAA Authorization: To maximize recruitment strategy, we request a waiver of HIPAA authorization to access electronic medical records to identify eligible participants (prior to Visit 1). In identifying participants, there is no more than minimal risk; we will only be reviewing medical records to identify eligibility. Identifiers will be removed at the earliest opportunity. Any protected health information collected will be de-identified when entered into the secured study database (as described above – **Section H.1.1**).

The research could not be practicably carried without the waiver, because identifying participants prior to Visit 1 is necessary to identify potentially eligible participants so that he/she can be approached by the research team member immediately after visit with surgical oncologist. This creates the least disruption in clinic to the patient and providers. Without a waiver of consent for screening participants prior to their clinical visit, the recruitment of participants will be greatly hindered and their privacy may be more profoundly impacted. It would not be feasible to approach every patient in clinic, perform consent procedures and then determine eligibility. In addition, ineligible participants may be disturbed unnecessarily. The research coordinator will discreetly approach patients after scheduled clinic visit and will invite them to private area to discuss possibly study participation. Adequate written assurances exist in order to ensure identifiers will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the identifiers would be permitted under the Privacy Rule, because only identified team members, such as co-investigators and other research team members (e.g., research coordinators, project manager) listed on the Delegation Log of Authority will have access to study database.

H.3.2 Study Withdrawal/Premature Discontinuation of Subjects: The subject may withdraw consent for participation in the study at any time without prejudice. Additionally, the Investigator may withdraw a subject if, in his/her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

A subject's participation in the study may be discontinued and the subject withdrawn for any of the following reasons:

- The subject wishes to withdraw from the study
- Request by a regulatory agency (e.g., Institutional Review Board/Independent Ethics Committee)
- Subject experiences generalized impairment or mental incompetence that is worsened compared to baseline and that would result in the subject being unable to understand his or her participation in the study
- If, in the Investigator's medical judgment, further participation would be injurious to the health and well-being of the subject, or is not in the best interest of the subject
- Administrative reasons, such as subject non-compliance or a major protocol violation

Overall, all subjects will be followed to the extent possible. The reason(s) for a subject's removal from study will be clearly documented in the source record and on the appropriate eCRF with the specification of reason for discontinuation. Study withdrawal will include final assessments as required by protocol and every effort will be made to perform the study follow-up procedures. Any subject prematurely removed from the study for any reason will be followed, to the best extent possible for as long as possible. This information will be used in the final analysis of data to determine if there is any bias in the final results.

H.4 Safety

H.4.1 Stopping guidelines: The trial can be prematurely closed by the PI in consultation with the responsible biostatistician for the following reasons:

- It appears that patients' enrolment is unsatisfactory with respect to quality or quantity, or data recording is severely inaccurate or incomplete.
- There is external evidence demanding a termination of the trial, e.g., indicating that the rate or severity of serious adverse events or morbidity in this trial poses a potential health hazard caused by the trial

treatment in one or both of the trial groups.

H.4.2 Safety monitoring: Subjects will be routinely monitored at regular study intervals (**Table 1**) for signs of adverse events. Safety surveillance will begin at consent. Adverse events will be captured starting with **Visit 3** (after surgical resection) and continue to the follow-up period. Safety monitoring will include physical examinations, concomitant therapies/medication, vital sign measurements, infectious disease status, assessment of adverse events performed at specified time points during the study. In concordance with routine care, participants will be followed for a total of 6 months after date of surgery.

H.4.3 Safety evaluation/reporting adverse events: An adverse event is defined as any untoward medical occurrence in a patient that does not necessarily have a causal relationship with the trial treatment (NPWT) and that occurs after the surgical procedure through visit 6. The following exceptions are predefined in the study protocol and will not be recorded as adverse events: (1) occurrence of SSI is assessed as outcome measure only (not as an adverse event); (2) any adverse event that is expected during the postoperative course or the underlying disease (e.g., pain, nausea, vomiting, hypertension, hypotension, imbalances of blood sugar or electrolytes or other laboratory values out of range), and that does not exceed Grade I of the Dindo-Clavien classification of postoperative complications.[37,38] All unexpected events and events exceeding Grade 1 of the Dindo-Clavien classification or the NCI's Common Terminology Criteria for Adverse Events version 5.0 will be recorded on the adverse event log.Grade 1 expected events will not be recorded on the adverse event log or the adverse event CRF. Laboratory values out of range at Grade 2 or higher will be recorded on the adverse event log starting with Visit 5 (post-operative follow up) and continue to the follow-up period. Only clinically significant adverse events will be recorded on the adverse event CRF.

From the postoperative period until the final visit (**Visit 7**) or until premature withdrawal of the patient, all serious adverse events will be documented on a serious adverse event form. A serious adverse event will be defined as an event that results in death, is immediately life-threatening, requires or prolongs hospitalization, or results in persistent or clinically important disability or incapacity, as judged by the investigator or designated sub-investigator. Serious adverse events will be classified by intensity (mild, moderate, severe), outcome (ongoing, recovered completely, recovered with sequelae, death, unknown) and causality (unrelated; possibly, probably or definitely related to trial intervention; not assessable). The assessment is based on clinical findings and needs to be made by the investigator or designated sub- investigator. Serious adverse events will be reported within 7 days after becoming known.

H.4.3 Safety oversight: Serious Adverse Events: Serious Adverse Events (SAEs) from this protocol will be reported to IRB. The Protocol Monitoring Committee (PMC) will review these SAEs in accordance with the protocol-specific DSMP (**APPENDIX I**). This trial will be continuously monitored by the PI and the research team and reviewed at monthly. Safety and monitoring reports will be managed by the CRO and will be made available to the PMC or appropriate monitoring body by designated members of the PMC or the study statisticians. This protocol will be subject to periodic internal audits based on risk or as recommended by the PMC.

H.5 Study Monitoring: Study will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly by the MCC Clinical Monitoring Core for accuracy, completeness, and source verification of data entry, validation of appropriate informed consent process, reporting of SAEs, and adherence to the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

H.6 Data Management: Data collection is the responsibility of the clinical trial staff at under the supervision of the PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All required information collected during the trial will be entered in a case record form by the PI or a member of the research staff. Documentation is expected to be completed as soon as possible after information has been collected. The investigator is responsible for the accuracy of the documentation and must ensure that all entries can be verified by source data. An explanation must be given for all missing data. Data will be captured in OnCore and/or Moffitt's electronic Clinical Trials Management System. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. For each subject enrolled, the electronic CRF (eCRF) must be completed by the assigned data manager or other

authorized study staff. Any paper forms should be typed or filled out indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his/her authorized delegate. This also applies to records for those subjects who fail to complete the study. If a subject withdraws or terminates from the study, the dates and reasons must be noted on the CRF.

H.6.1 Data Quality Assurance: The PI will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Collected data will be subject to electronic and manual quality assurance procedures. Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the PI and research team for clarification/resolution. Following written Standard Operating Procedures (SOPs), the internal monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP).

H.6.2 Study Files and Document Storage: The PI will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. The Investigator's study file will include the following (as applicable): the protocol and protocol amendments, eCRFs, query forms, IRB/IEC and governmental approval with correspondence, sample informed consent, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Study documents should be retained for a minimum of 10 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 10 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations.

H.6.3 Protocol Deviations: A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH GCP:

- Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2

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Appendix I

Data & Safety Monitoring Plan for
Randomized Trial of Prolonged Use of Negative Pressure Wound Therapy in Patients Undergoing Surgical Procedures for the Management of Gastrointestinal Malignancies

A. Identification of oversight responsibility:

1. The PI has primary responsibility. Please identify who will provide oversight for the monitoring plan of this study. *(Check one)*
   ☒The MCC Protocol Monitoring Committee (PMC)
   ☐The MCC multi-center external Data & Safety Monitoring Board (DSMB) (for multi-institutional high- and medium-risk studies)
   ☐A sponsor identified Data and Safety Monitoring Committee or medical monitor *(identify)*
   ☐Other *(identify)*

2. At what point during the study will adverse events begin to be identified?
   ☐After obtaining informed consent
   ☐At start of treatment
   ☒Other *(identify and specify):* 3-5 days post-surgery (Visit 3)

3. How often will the responsible oversight body meet? What will be reviewed? (e.g., adverse events, accrual, protocol violations, and audit results) What information will be required in reports? *(check one)*
   ☒MCC PMC: The PMC meets monthly and reviews accrual, patterns and frequencies of all adverse events, protocol violations and when applicable, internal audit results.
   ☐Other
   ☐External DSMB: _____

B. Description of internal (PI) safety review and monitoring process:

1. Who will be responsible for identifying adverse events? *(check all that apply)*
   ☒PI
   ☐Disease specific team: *(identify)*
   ☐Other medical professional(s): *(identify and specify relationship to protocol):*

2. Who will review adverse events? *(check all that apply)*
   ☒PI and Co-PI
   ☐Disease specific team: *(identify)*
   ☐Other medical professional(s): *(identify and specify relationship to protocol)*

3. How often will the review occur?
   ☒Monthly
   ☐Weekly
   ☐Other: *(specify)*

4. What will be reviewed? *(check all that apply)*
   ☒Adverse events in aggregate, by attribution (expected or unexpected)
   ☒Relationship to study drug/intervention
   ☐Application of dose finding escalation/de-escalation rules
   ☒Application of study designed stopping/decision rules
   ☒Whether the study accrual pattern warrants continuation/action
   ☒Protocol violations
   ☐Other: *(specify)*

Appendix I

C. Description of a structured adverse event determination and reporting system:
(If numbers 1-3 are detailed in a protocol specific adverse event reporting section or appendix, the PI may append that section and proceed to number 4. If not, PI may revise the example of AE and SAE definition provided below and the table provided below for AE reporting.)

1. Provide definitions of adverse events (AE)/serious adverse events (SAE): *(see appendix for an example and revise based upon protocol specifications)*

   Please see **Section H.4.3** of protocol

2. What AEs are expected or have been reported nationally with this study or with related trials or procedures?

   There is no reported increased incidence of wound complications with the use of the NPWT dressing. No additional risks for study participants are anticipated, since the safety and feasibility of the application of NPWT on postoperative wounds has been established in several previous studies.`

3. How will AEs be classified/graded?
   ☒NCI Common Toxicity Criteria, version 2.0, or NCI Common Toxicity Criteria for Adverse Events, version 3.0 or 4.0, as appropriate.
   ☒Other: NCI Common Toxicity Criteria for Adverse Events version 5.0

4. How and to whom will AEs be reported? What is the time table for reporting AEs to the clinical research coordinator (CRC), IRB, responsible monitoring body, and where appropriate, to FDA, NIH and sponsor? *(check one)*
   ☒If the protocol will be managed through the Cancer Center CRO, PI or PI designate will report all adverse events to CRO. The CRO will report SAEs to the IRB. The NIH, FDA and study sponsor will receive the reports from the PI or PI designee as appropriate. AE information will be entered into the CRO database. AE information will be managed by the CRO and will be made available to the PMC or appropriate monitoring body by designated members of the PMC or the study statisticians.

   ☐For studies that are program run or conducted at an affiliate site, the program staff or Affiliate Office will report all AEs directly to the IRB per local IRB reporting policy and per study guidelines to the NIH, FDA, or study sponsor with a copy to the CRO for purposes of protocol tracking. *(Include timetable information)*. The Principal Investigator will be responsible to report offsite affiliate AEs that occur to the PMC.

D. Description of protocol specific data capture:
1. How will the data be collected? *(Check all that apply)*
   ☐AE forms
   ☒Protocol specific case report forms
   ☒Other: *(specify)*Data will be entered into electronic database

2. How will AEs be captured? *(check all that apply)*
   ☒Lab tests/physical exam
   ☒Patient interviews: in-person study visits
   ☒Phone follow-up
   ☐Other: *(specify)*

3. How will data be managed and made available for review?
   ☒CRO will manage the trial: Data will be collected using disease-specific criteria on case report

forms.

☐Protocol specific data will be entered into the clinical research database for in-house trials.

☐Protocol specific data will be submitted to the sponsor.

☐Data will be submitted by the P1 or protocol team to the sponsor at least:

- ☐Weekly
- ☐Monthly
- ☐Other *(specify)*

☐Other: (provide description of case report forms, data management and submission)