MSK PROTOCOL COVER SHEET

A Phase III Randomized Controlled Trial of Negative Pressure Wound Therapy in Post-Operative Incision Management

PI: Mario Leitao, MD

Department of Surgery

Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Recent changes in the surgical patient population, including patients with varying levels of obesity and significant comorbidity, have generated many questions regarding the optimal management of post-operative wounds. Negative pressure wound therapy (NPWT) at the time of laparotomy closure has been described as a means to aid in the healing of complex wounds through increased efficiency of healing and decreased risk of wound complications. To date, however, evidence supporting its use, and justifying its expense, remains limited. Studies have centered around specific patient populations, and resulted in conflicting outcomes.

We propose to conduct a randomized controlled trial of post-operative wound management with use of the Prevena Incision Management System, a subtype of the V.A.C.® negative pressure wound therapy system (KCI, San Antonio, TX). We believe that a negative pressure wound therapy device placed at the time of wound closure may help reduce the rate of complications and post-operative morbidity. Our population includes women undergoing laparotomy for gynecologic cancers and morbidly obese women undergoing laparotomy for any reason. We will randomize them into two groups; one group will receive placement of the Prevena system over clean or clean-contaminated, closed incisions, and the other group will receive a standard dry gauze dressing over their clean or clean-contaminated, closed incisions.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

- **Primary objective**: To determine if prophylactic use of a NPWT system on clean or clean-contaminated, closed incisions reduces incidence of post-operative wound complication which includes at least one of the following: wound separation as diagnosed by gross observation, wound seroma or hematoma as defined by the clinical or radiographic presence of fluid or blood collection in wound, and wound infection as defined by the presence of purulent discharge requiring exploration and/or cellulitis requiring the use of antibiotics, in patients with gynecologic malignancies undergoing laparotomy, and morbidly obese women undergoing laparotomy for any reason.
- **Secondary objective**: To determine the impact of NPWT on the incidence of specific type of wound complication as listed above.
- **Tertiary objective**: To report the incidence of adverse events such as blistering and contact dermatitis associated for each arm as per the published MSK Secondary Surgical Events system (Appendix D).

3.0 BACKGROUND AND RATIONALE

Wound healing is a complex physiologic process. Structural and functional disruption of the skin and underlying soft tissue results in the initiation of a sequence of events that includes hemostasis, inflammation, proliferation, and, ultimately, maturation of epithelial and sub-epithelial tissues.[1] Surgical wounds are also subject to this orderly process of healing. Post-operative incisions are typically characterized on the basis of their perceived contamination. [2] The Centers for Disease Control (CDC) classifies surgical incisions as clean, clean-contaminated, contaminated, or dirty.

Table 1: Surgical Wound Classification [36]

Class I/Clean:	An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet the criteria.
Class II/Clean-Contaminated:	An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.
Class III/Contaminated:	Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered are included in this category.
Class IV/Dirty-Infected	Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

Management of surgical wounds is often based on these final categorizations at the time of surgery, and the known effects of surgical site contamination on the physiologic process of wound healing. Typically, surgical wounds classified as clean and clean-contaminated are closed primarily at operative completion. Incisions categorized as contaminated or dirty are often allowed to heal through secondary intention, wherein the wound is left open and allowed to granulate and seal over a longer duration of time. This serves as a means to prevent dysregulation of the healing process and such sequelae as infection, seroma formation, or skin necrosis.

More recently, additional changes in the surgical patient population, including more patients presenting with various levels of obesity and significant comorbidities, have generated new questions about the optimal management of post-operative wounds.[3] One relatively new innovation is negative pressure wound therapy (NPWT). First described in the 1990s, NPWT was introduced to aid in the healing of complex wounds. NPWT is a non-invasive therapy that exerts a mechanical vacuum force on tissue, drawing out exudate and simultaneously working to attract wound edges centripetally; these actions theoretically accelerate the healing process.[4] Physiologically, NPWT is thought to increase the peripheral blood flow in the disrupted tissue, thereby improving local oxygenation and promoting angiogenesis and proliferation of healthy granulation tissue. A 2014 study by Wang et al demonstrated

increased levels of intracellular adhesion molecule-1 (ICAM-1), migratory inhibitory factor (MIF), vascular endothelial growth factor (VEGF), and collagin I in animal models treated for traumatic wounds with NPWT.[5] Additional translational studies have corroborated these findings.[6]

NPWT was first used clinically in burn and graft patients, with later adoption in patients with orthopedic, diabetic, and trauma wounds. The majority of literature evaluating the use of NPWT alone and in comparison to various other "standard" wound dressings is comprised of case series and retrospective cohort studies.[7-22] In the earliest randomized controlled trial, the results of which were published in 2006, Llanos et al evaluated 60 patients with burn wounds with sufficient skin loss to hinder primary closure.[23] Patients were randomized to placement of NPWT wound vacuum-assisted closure (VAC) at -80 mmHg suction versus VAC placement without application of suction. Final analysis demonstrated the NPWT cohort to have an improvement in graft outcome as well as a decreased duration of hospital stay. Similar results were seen in a 2011 prospective study by Petkar et al, with increased graft take in this patient population.[24]

Other primary endpoints of seroma formation, wound dehiscence, and surgical site infection have been evaluated in patients receiving NPWT. A 2011 prospective trial by Pachowsky and colleagues randomized 19 men and women who had undergone total hip arthroplasty to prophylactic wound vac versus standard dry dressing and demonstrated a decrease in post-operative seroma in patients with the wound vac in situ.[25] Stannard et al evaluated a larger prospective cohort of 249 patients after orthopedic surgery and showed a decreased incidence of wound dehiscence amongst patients utilizing NPWT.[26] Most recently, a non-randomized prospective analysis of 150 patients undergoing cardiac surgery with median sternotomy demonstrated a 12% decrease in surgical site infection in those patients given a prophylactic wound vac.[27]

Despite the favorable results of these described trials, an equal number of similarly well-designed studies have demonstrated opposite findings. Randomized controlled trials in the fields of plastic and orthopedic surgery as well as otoloargynology have shown no difference in wound outcomes or rates of incisional drainage, infection, or dehiscence.[28-32] Furthermore, a 2011 randomized trial by Dorafshar et al demonstrated a significantly increased cost to the use of NPWT over standard dressings: $96 daily for patients in the vac arm as compared to $4 daily for patients receiving standard gauze dressings.[29] Two more recent cost-benefit analyses, however, illustrated a potential cost savings with the use of NPWT due to the decreases in rates of wound complication and surgical site infection.[33, 34] Echebiri and colleagues posited a prophylactic wound vac cost benefit with SSI rates exceeding 14%.[33] Lewis et al concluded that risk of wound complications must be reduced by 33% for prophylactic NPWT to be a cost effective intervention.[34] To date, there does not exist a consensus on the benefit of NPWT and it is used at the provider's discretion. Given the clear need for optimization of post-operative wound management, as well as the high costs of wound vac therapy, further investigation is warranted.

Currently, there exists a number of options for wound vacuum-assisted closure. Some institutions create their own NPWT device through tubing attachments to standard gauze

dressing. The PICO system (Smith and Nephew Healthcare, Hull, United Kingdom) is a NPWT that is meant for single, short duration use. The most frequently utilized, and studied, however, is the KCI V.A.C.® negative pressure wound therapy system (KCI, San Antonio, TX). The KCI V.A.C.® is comprised of a closed, sealed system that applies wound suction through the use of an open-celled foam covered with occlusive tape. Intermittent or continuous suction is maintained through tubing that is connected from the foam to a vacuum pump. The standard rate of negative pressure is -125 mmHg. The V.A.C.® therapy platform includes a number of different products for various clinical indications. The Prevena Incision Management System (V.A.C.® Therapy, KCI USA, Inc., San Antonio, TX) is one device intended to manage the environment of clean closed surgical incisions through the removal of wound drainage and exudate via the application of NPWT. The Prevena system is applied immediately post-surgery to the clean closed incision and allowed to remain in place for 2-7 days.

We propose conducting a randomized controlled trial of post-operative wound management with use of the Prevena Incision Management System. We believe the application of a negative pressure wound therapy device placed at completion of surgery may help reduce the rate of surgical site infection and post-operative morbidity. The need for prospective data, particularly in the oncologic community, is significant, and this device can potentially have wide ranging benefits to patients. In addition, the hospital will benefit from the knowledge acquired in this study; given that Prevena Incisions Management System is costly, it should not be adopted for use if it does not prove beneficial to patients. .

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a randomized phase III study of patients undergoing laparotomy for either gynecologic malignancies or any indication in patients with a BMI $\geq$40. At Hartford Healthcare, this study will be performed on gynecological cancer patients only. The objective is to determine if prophylactic use of a NPWT system on CDC-defined clean or clean-contaminated, closed laparotomy incisions reduces the incidence of post-operative wound complications.[36] Clinicodemographic variables of interest will be recorded as listed below. All patients enrolled will undergo standard wound closure; this entails fascial closure with PDS suture and a stapled skin closure. Pre and intra-operative details will be collected as described in Table 2. Incidence of inpatient post-operative wound complications will be documented through the use of an inpatient data collection sheet (Appendix C) that will be completed by a provider on the day of day of discharge or post-operative 7, whichever occurs first; these complications are listed in Table 2. Of note, all patients who randomize to the treatment arm are required to have the Prevena system in place for a minimum of 2 days up to a maximum of 7 days. Patients who randomize to the standard dry gauze arm will have their dressing removed on post-operative day 2 (or sooner if clinically indicated). Length of stay will also be captured for each patient. For laparotomy procedures length of stay is routinely a minimum of 2 days [37], thus proving no foreseeable problem with a 2-day minimum placement of the Prevena system nor incurring a greater length of hospital stay. Incidence of outpatient post-operative wound complication will be documented through the use of an outpatient data collection

sheet that will be completed by a provider at the time of the routine post-operative follow-up visit, which will occur at 30 days +/- 5 days after the day of surgery as well as through ongoing documentation of events as elicited through the institution's standard reporting system to collect information on enrolled patients. At Memorial Sloan Kettering Cancer Center (MSK), this system includes routine post-operative phone calls from nursing staff and 24 hr MD availability via the MSK urgent care center and gynecologic fellows for outpatient telephone communication. Incidence of wound complication as previously defined will be an ongoing assessment throughout the 30 day trial period and not captured as separate endpoints for any particular time.

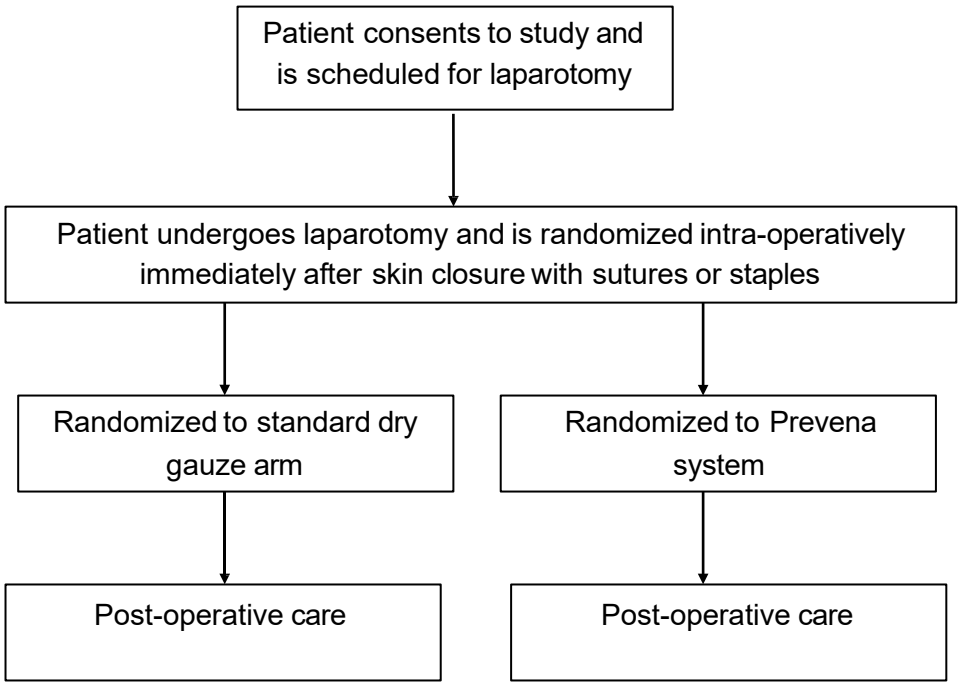

Table 2: Pre-/Intra-/Post-Operative Patient Assessment

	Pre-operative	**Intra-operative**	**Post-operative (inpatient)**	**Post-operative (outpatient)**
Hemoglobin	x			
Serum albumin	x			
PTT/PT/INR (optional, but preferred)	x			
Indicate if bowel resection was performed		x		
Wound type classification		x		
Transfusion		x		
Estimated Blood Loss		x		
Length of surgery		x		
Presence of ascites		x		

Total IV fluid for first 24 hours			x	
Wound infection			x	x
Wound separation			x	x
Wound seroma			x	x
Wound hematoma			x	x
Wound blistering			x	x
Wound contact dermatitis			x	x

Table 3: Timing of Patient Evaluation by Event

	Inpatient	Outpatient
Time of NPWT removal	Day of discharge vs POD 7, whichever occurs 1st*	
Post-operative follow-up visit		30 days +/- 5 days post-operative**

*Vac must remain in place for a minimum of 2 days.

**If the patient cannot be seen before POD 35 for a post-operative follow-up visit, a phone call placed by a study investigator may be substituted for the visit (see section 4.2)

POD, post-operative day; NPWT, negative pressure wound therapy.

4.2 Intervention

We propose the use of the Prevena Incision Management System, a subtype of the the V.A.C.® negative pressure wound therapy system (KCI, San Antonio, TX), for patients randomized to the intervention arm of our study.

The Prevena Therapy System will be applied at the time of wound closure in a sterile field for all patients who have undergone laparotomy, meet study inclusion criteria, and are randomized after the time of skin closure to the intervention arm of the study.

- The Prevena system will be left on for a minimum of 2 days and up to a maximum of 7 days as per product manufacturer recommendation.
- The Prevena system will be removed on the day of day of discharge or post-operative day 7, whichever occurs first.
- Patients who randomize to the standard dry gauze arm will have their dressing removed on post-operative day 2 (or before if clinically indicated)
- Evaluation for wound complications will be performed through provider-completed data collection sheets on the day of discharge (or POD 7), at the time of the Prevena system removal. Another evaluation will be performed during the patient's routine post-operative visit, which will occur at 30 days +/- 5 days after the day of surgery. Ongoing evaluation and documentation via phone calls, ugent care visits and nursing

follow-up, as per institutional guidelines, are in place to collect information throughout this time period.

- Patients who are unable to return for their post-operative visit before POD 35 will be contacted via telephone by a study investigator to complete a wound assessment based on what the patient reports.
- Patient follow-up will cease at the time an "event" is documented even if prior to the planned 30-day follow-up period. An event refers to one of the following:
    - Wound infection
    - Wound separation
    - Wound seroma
    - Wound hematoma

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

The Prevena Incision Management System is an FDA-approved negative pressure wound therapy device marketed and sold in the U.S. It is intended to aid in the healing of clean or clean-contaminated, closed surgical incisions by allowing for ongoing drainage through the maintenance of a closed environment and continual removal of exudate. The Prevena™ Customizable™ dressing system consists of a self-adhesive foam dressing with a unique configuration to allow the clinician to alter the dressing to cover closed surgical incisions of different sizes and shapes, including linear incisions >20 cm. The foam is a polyurethane coated, polyester fabric interface layer impregnated with 0.019% ionic silver that serves a similar function as the traditional non-adhering V.A.C. GranuFoam Dressing whilst protecting the skin from direct contact with the foam bolster. A polyurethane film with acrylic adhesive provides adhesion of the foam to the skin surrounding the incision. Hydrocolloid on either side of the foam aids in securing it to the skin. The Prevena™ Customizable™ dressing is intended for use with the Prevena 125 Therapy Unit to maintain negative pressure. The Interface Pad used with the Prevena Customizable Dressing also has the built-in pressure indicator which, when compressed, indicates that negative pressure in the system is between -75mmHg to -125mmHg (ideal). A raised pressure indicator button indicates that the negative pressure is less than -75mmHg. The Prevena 125 Therapy Unit delivers 7 days of continuous negative pressure at -125 mmHg through the dressing to the incision site and is battery powered and portable. All patient-contact materials are latex-free.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Criteria for Eligibility Prior to Surgery

6.1.1 Subject Inclusion Criteria

- Women of any BMI undergoing a laparotomy procedure for a presumed gynecologic malignancy **or** women who are morbidly obese (BMI$\geq$40) undergoing laparotomy for any indication
- Age $\geq$18

6.1.2 Subject Exclusion Criteria

- Women undergoing panniculectomy at the time of laparotomy
- Women with sensitivity to silver

6.2 Criteria for Eligibility During Surgery

6.2.1 Subject Inclusion Criteria

- Same as 6.1.1

6.2.2 Subject Exclusion Criteria

- Women with laparotomy incisions left open due to case classification as "contaminated" or "dirty"
- Women with laparotomy incisions unable to be closed primarily due to tissue or fascial damage

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or a member of the research teams at MSK and Hartford HealthCare. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study. Patients identified in this manner would subsequently be approached for study enrollment after consultation with their treating physician. This limited waiver will apply only to MSK. Any participating sites that require a limited waiver must obtain it from their own local Privacy Board (PB) via a separate protocol addendum or request. It is the responsibility of the MSK staff to confirm the participating data collection site(s) have a limited waiver approved by their local IRB(s)/PBs.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary for the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSK in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator, or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information

relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

Potential study participants who meet our basic inclusion/exclusion criteria will be approached by their physician to volunteer for this study. If the patient indicates a willingness to participate, a consenting professional will explain the study in detail. Women who volunteer and sign an informed consent will then be randomized intra-operatively to either the intervention arm (in which case they will receive immediate post-operative placement of the Prevena Incision Management System) or to the non-intervention arm (in which case they will receive standard dry gauze dressing at the completion of surgery). The goal is to obtain 686 randomized patients. We expect that about 515 of these patients will recruited from MSK. The others will be recruited from the participating sites.

8.0 PRETREATMENT EVALUATION

Routine evaluation with a baseline history and physical exam prior to surgery is mandatory with documentation of the following clinicodemographic variables as listed below. Pre-operative laboratory testing is also required prior to surgery with required laboratory studies listed below. Standard time frames (30 days) for pre-operative testing will be used for study participants.

Clinicodemographic variables of interest:

- Age
- BMI
- History of hypertension
- History of diabetes mellitus
- History of vascular disease
- History of chronic pulmonary disease
- History of chronic liver disease
- History of chronic kidney disease
- Diagnosis of cancer
- History of prior abdominal surgery including type of prior abdominal surgery: laparotomy vs minimally invasive
- History of smoking, current or past
- History of alcohol use, current or past
- Steroid use within 30 days
- History of radiation therapy within 60 days
- History of chemotherapy administration within 60 days

Required pre-operative laboratory tests (for collection and analysis only):

- Hemoglobin
- Serum albumin

- PTT/PT/INR (optional, but preferred)

9.0 TREATMENT/INTERVENTION PLAN

- Patients who are randomized to the intervention arm of our study will undergo planned laparotomy with routine primary closure of their surgical incision at the completion of the case. Staples will be used for skin closure after standard fascial closure with PDS suture.
- Immediately thereafter, the experimental Prevena Therapy System will be applied to the closed, clean or clean-contaminated surgical incision.
- The Prevena™ Customizable™ dressing will then be connected to the Prevena 125 Therapy Unit to maintain a constant negative pressure of -125 mmHg.
- The Prevena system will be left on for a minimum of 2 days and up to a maximum of 7 days while the patient remains in the hospital post-operatively.
- All Prevena systems will be removed on the day of discharge or post-operative day 7, whichever occurs first.
- Evaluation for wound complications will be performed through provider-completed data collection sheets. These evaluations will be performed on the day of discharge (or POD 7 at the time of Prevena system removal) and at the patient's routine post-operative visit, which will occur at 30 days +/- 5 days after the day of surgery.
- Ongoing evaluation and documentation via phone calls, urgent care visits and nursing follow-up are in place to collect information throughout this time period as per institutional guidelines.
- Patients who are unable to return for their post-operative visit before POD 35 will be contacted via telephone by a study investigator to complete a wound assessment based on what the patient reports.
- Patient follow-up will cease at the time an "event" is documented even if it occurs prior to the planned 30-day follow-up period. An event refers to one of the following:
    - Wound infection
    - Wound separation
    - Wound seroma
    - Wound hematoma

10.0 EVALUATION DURING TREATMENT/INTERVENTION

- Evaluations will be made via observational assessment for the presence or absence of various clinical features and diagnoses as depicted below in tabular form (Table 3). Intraoperative assessments will be collected prospectively by research study assistants assigned to this protocol. Diagnoses of wound complications for both study arms will be collected on the day of discharge or post-operative day 7, whichever occurs first, as well as throughout the outpatient time period and at the time of the post-operative follow-up visit that will occur at 30 days +/- 5 days after the day of surgery. A wound complication as previously defined will be treated as an event at any point during the 30+/5 day follow-up period, no separate endpoints within the trial time will be created for analysis purposes.

Table 4: Observation Variables During Treatment

	Intra-operative	Post-operative (DOD or POD7)	Post-operative (POD 30 +/- 5)
Indicate performance of bowel resection	X		
Wound type classification	X		
Use of transfusion	X		
Presence of ascites	X		
Estimated blood loss	X		
Length of surgery	X		
Total IV fluid for first 24 hours		X	
Wound infection		X	X
Wound separation		X	X
Wound seroma		X	X
Wound hematoma		X	X
Wound blistering		X	X
Wound contact dermatitis		X	X

DOD = Day of discharge; POD = Postoperative day

11.0 TOXICITIES/SIDE EFFECTS

Risks Due to PREVENA ™ Incision Management System

Risks	Disorders/Conditions
Skin and Subcutaneous Tissue	• Local cutaneous reaction (i.e. redness, rash, significant pruritis, urticaria) • allergic reaction • maceration • minor soft tissue damage • epidermal (skin) stripping • minor bleeding • pain • contusion (bruising)
Other	• bleeding complications (associated with the surgical procedure, concomitant therapies and co-morbidities) • first degree burn (if device gets warm) • exposure related infection • localized infection • physical discomfort • minor desiccation (due to dressing leak) • moderate soft tissue damage (i.e. due to trip hazard, tubing entanglement) • deterioration of the wound (due to lack of visibility of incision site through dressing)

With severe or persistent side effects, treatment with the Prevena system will be discontinued.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary outcome is the observed reduction of wound complications which includes at least one of the following:

- Wound separation as diagnosed by gross observation
- Wound seroma or hematoma as defined by the clinical or radiographic presence of fluid or blood collection in wound
- Wound infection as defined by the presence of purulent discharge requiring exploration and/or cellulitis requiring the use of antibiotics.

Secondary outcomes of wound blistering and contact dermatitis as related to adverse effects of either dressing.

Grading for complications will be captured as per the published MSK Secondary Surgical Events system (Appendix D) and documented for all cases of wound complication.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from the study for any of the following reasons but they will not be replaced (see ntention to treat analysis below):

- If at any time the patient is found to be inevaluable for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (e.g., a change in diagnosis), she will be removed from the study.
- If the patient decides to withdraw consent or discontinue participation in the study, she will be removed from the study; however, the Prevena will only be removed for medical reasons and not because the patient is withdrawing from the study.

The following patients will come off study, but they will be included in the analysis:

- If the Prevena Incision Management System is removed prior to 2 days after initial placement, the patient will be included in the analysis as a failure.
- If the patient experiences any grade 4 toxicity as per the MSK Secondary Surgical Events system.

14.0 BIOSTATISTICS

An institutional database with information regarding surgical procedures performed by the GYN service at MSK was queried after the institution of a surgical site infection (SSI) reduction bundle in January 2015. Data for the period between 1/1/15 and 6/30/15 demonstrates a total of 248 laparotomies performed for all malignant indications and benign indications for patients with a BMI $\geq$40 on the gyn service. 19 cases of wound complication

were noted resulting in a rate of 7.6%. We have chosen a baseline wound complication rate of 10% to take into account potentially higher rates of wound complications in alliance sites that have not yet incorporated an SSI reduction bundle.

Given our known yet unpublished rate of wound-related complications in morbidly obese patients undergoing laparotomy of 27%, it is also important to include this patient population with a clear elevated rate of wound morbidity in our study, even if it will only represent ~1% of our total cases.

With a baseline rate of 10%, we would choose a 50% decrease in the rate of complication to 5% as clinically significant. To achieve 80% power with a type I error of 10% (2 sided test), we will need to enroll a total of 686 patients. Data from our department demonstrates ~38 eligible laparotomies at MSKCC main campus per month. Over the course of the year, this would result in 456 eligible cases per year. If only 30% of eligible patients chose to enroll on study, this would result in 137 patients accruing yearly, which would require 5 years to complete the study.

The primary objective analysis of our study will be performed via a two sample test for binomial proportions to compare the difference in proportions between the 2 arms at a type I error of 10%. We will also estimate the proportion of patients with post-op wound complication within 30 days and 90% Confidence interval for each arm assuming binomial proportions. We will perform an intent to treat (ITT) analysis where all patients who were randomized will be included in the analysis in the arm they were randomized to. If the Prevena Incision Management System is removed prior to 2 days after initial placement, the patient will be included in the analysis as per ITT and they will be considered as failures. We expect that <5% of the enrolled patients will have the Prevena system removed prior to 2 days after placement. All patients who were randomized will be evaluable for the analysis except patients that require abdominal reoperation within 30 days to address a postoperative complication unrelated to the surgical wound or patients whose BMI is less than 40 who are found to have benign pathology following their surgery. These patients will be considered non-evaluable for primary endpoint. Patients that require any surgical intervention within 30 days specifically to address a wound related complication will be considered evaluable. Patients removed from the study for reasons listed in Section 13 will be included in the analysis as per ITT principle. We will continue accrual until 686 evaluable patients are randomized.

Interim Analysis: The study will be terminated if either the futility or efficacy boundaries are crossed at the interim analysis when 343 evaluable patients have been randomized. The boundaries for the Z-test statistic after half patients (n=343) are enrolled and randomized when the interim analysis will occur are +/-0.246 for futility and +/- 2.538 for efficacy. At the end of the study the boundaries will be +/-1.662.

This secondary objective analysis will analyze each type of complication separately namely wound infection, separation, and formation of seroma or hematoma, in a logistic model where the outcome is the presence and absence of wound complication and the covariate of

interest is the intervention arm (A or B). This analysis will be hypothesis generating as we expect very low rates of each one of these outcomes. P-values will not be adjusted for multiplicity.

For the tertiary "safety" objective, we plan to report the incident of adverse events such as blistering and contact dermatitis associated for each arm separately, as defined by the CTCAE v4.0.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming that the participant is eligible to enroll in the study. Although confirmation of Part II eligibility will be documented by the surgeon in the operative report, the Part II Eligibility Checklist may be signed by the surgeon within 5 business days post-surgery, as the surgeon will be scrubbed into the procedure and unable to sign in real time. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

Patients will be randomized (1:1) to either arm A (placement of Prevena wound vac) or arm B (standard dry gauze dressing) immediately after skin closure after all eligibility criteria are established for patients who previously consented to the study. Randomization will be accomplished by the method of random permuted block stratified by BMI > 40 (yes, no). Sealed, opaque, non-resealable envelopes containing the assignment form will be used.

16.0 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into the MSK Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record. All efforts will be made to ensure maintenance of patient confidentiality and HIPAA compliance. All data will be maintained on the MSK Clinical Research Database and the Protocol Management System. All data collected will be stored on a secure server at MSK and access will be password protected. This server will only be accessible by trained study investigators.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team at a minimum of two times per year, and more frequently if indicated.

Research Staff will verify eligibility, informed consent, and accuracy of the demographic data collected for all patients whenever a patient is enrolled onto the study. This will ensure the quality of the data collected and verify the presence of all pertinent study data and documents.

16.2 Data and Safety Monitoring

The study investigators will be responsible for ensuring the safety of the study participants. The investigators will stress the importance of reporting adverse events to the participants and the investigators will assess for adverse events at each instance of contact with the participants. Should adverse events occur, the study investigators will document these appropriately in the medical record and report these events to the IRB. CTCAE Version 4.0 will be used to assess adverse events.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials,” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSK were established and are monitored by the Clinical Research Administration. The MSK Data and Safety Monitoring Plans can be found on the MSK Intranet at: http://mskweb5.MSK.org/intranet/_assets/_tables/content/359709/DSMPlans07.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control. In addition, there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs: the *Data and Safety Monitoring Committee* (DSMC) for Phase I and Phase II clinical trials, and the *Data and Safety Monitoring Board* (DSMB) for Phase III clinical trials. These committees report to the Center’s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Every effort will be made to ensure the safety of our patients and the confidentiality of their medical information. During the enrollment and consent process, all risks, benefits, side effects, and alternatives will be discussed. Also, it will be stressed that this is a voluntary study and that the patient can withdraw without prejudice at any time.

Benefits and Risks: The potential benefit of this study is the determination of whether prophylactic use of negative pressure wound therapy can reduce the incidence of wound complications while maintaining a reasonable cost to the patient. Such a reduction in post-operative morbidity could potentially ameliorate a significant physical and emotional burden on the patient during the immediate post-operative period.

The risks of participation include the risks associated with wound vac placement; these include the uncommon but potential side effects of infection, bleeding, skin disturbance including maceration, breakdown, and blistering, and pain. There is also a potential risk of irritation or sensitivity to the foam, product adhesive, and/or tubing.

Alternatives: The current standard treatment option for patients eligible for this study would be surgery without post-operative prophylactic placement of a NPWT, and use of the standard dry gauze dressing instead. A patient's decision on whether or not to participate in this study will not affect the availability of standard, supportive, or other investigational treatment at MSK.

Costs: There will be no additional cost incurred by the patients who participate in the study.

Voluntary Nature of the Study: Participation in this study is entirely voluntary.

Inclusion of Children in Research: This protocol/project does not include children because the number of children who require surgical intervention for gynecologic malignancies is low. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

Patients will be informed of the extent of the risks, benefits, toxicities/side effects, alternatives/options for treatment, financial costs/burdens, and the voluntary nature of the study. The responsible investigator will ensure that this study is conducted in agreement with the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West, and Edinburgh amendments). The study will seek in every way to protect the rights of human subjects. No patient will be required to participate in the study, and participation or lack of participation will not affect the patient's subsequent care or treatment.

The patient will not incur any financial cost as a result of participation in the study. Participation will be entirely voluntary and subjects will not be reimbursed for participation in the study. Throughout the study, patient confidentiality will be maintained. No results of the

study will be presented or discussed in a fashion that will allow identification of a particular patient in the study. All adverse events will be fully disclosed to the IRB in a timely fashion as required.

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE. Additionally, Grade 1-4 events from the following list of protocol endpoint complications will be considered expected on study and not reportable as SAEs: wound seroma, wound hematoma, wound infection and wound separation.These will be tracked separately through the protocol data collection sheets.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

17.2.1 Other Reporting Requirements

All SAEs (regardless of causality) should be entered in the SAE tracker (Provided by KCI) and submitted every 3 months to Matthew Jacobs (Matthew.Jacobs@Acelity.com).

An SAE should be reported to Matthew Jacobs (Matthew.Jacobs@Acelity.com) within 24 hours of learning of the event, if the SAE is suspected to:

- Have caused or contributed to a death or serious injury; or
- The device has malfunctioned and suspected to contribute to a death or serious injury

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the

Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

A. KCI V.A.C. Clinical Guidelines

B. Prevena Incision Management System Product Monograph

C. Data Forms

D. MSKCC Secondary Surgical Events system