A Randomized Phase II Evaluation of Negative Pressure Wound Therapy for Reduction of Postoperative Surgical Site Infection in Patients Undergoing Colorectal and Hepatopancreatobiliary Surgery

Trial: NCT01905397

Protocol

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DUKE CANCER INSTITUTE

A National Cancer Institute-designated Comprehensive Cancer Center

A Randomized Phase II Evaluation of Negative Pressure Wound Therapy for Reduction of Postoperative Surgical Site Infection in Patients Undergoing Colorectal and Hepatopancreatobiliary Surgery

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LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
CRF	Case report/Record form
CRS	Colorectal surgery
DCI	Duke Cancer Institute
DUMC	Duke University Medical Center
FDA	Federal Drug Administration
HPBS	Hepatopancreatobiliary surgery
ICH	International Conference on Harmonization
I.V.	intravenous
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational new drug
IRB	Institutional Review Board
KCI	Kinetic Concepts, Inc
NPWT	Negative Pressure Wound Therapy
NSQIP	National Surgical Quality Improvement Program
REB	Research Ethics Board
PI	Principal Investigator
PIMS	Prevena™ Incision Management System
SAE	Serious Adverse Event
SOC	Safety Oversight Committee
SOP	Standard Operating Procedure
SSI	Surgical Site Infection
VAC	Vacuum Assisted Closure

1.0 INTRODUCTION

Surgical Site Infection (SSI) is a major source of morbidity in both colorectal (CRS) and hepatopancreatobiliary (HPBS) surgery. The SSI rate has been published to be between 20-35% [1-3]. Specifically, colectomy for the treatment of colorectal cancer is associated with a SSI rate of 10-30% [1] and hepatectomy for hepatocellular carcinoma has a SSI rate of 15-25% [4, 5]. Pancreaticoduodenectomy for pancreatic adenocarcinoma has a SSI rate of 10-20% [2, 6]. Taken together, up to a third of patients undergoing these complex abdominal surgeries will suffer the additional morbidity of SSI despite interventions such as appropriately timed and selected antibiotics. This added level of morbidity increases the complexity of patient care during recovery from surgery, lengthens post-operative hospitalizations and adds significant overall medical costs. Given these persistently high rates of SSI despite best practice standards, a low morbidity intervention such as the incisional wound vacuum assisted closure (V.A.C) system is an attractive technology to try to further improve SSI rates in these patients.

V.A.C® technology or negative pressure wound therapy (NPWT) has revolutionized the management of complex open wounds but its role in closed wounds remains undefined. Initial enthusiasm for its potential role in reducing SSI rates in closed laparotomy wounds came from a report in the cardiothoracic literature performed as a collaboration between Duke University Medical Center (DUMC) and the Durham VA Medical Center [7] . Negative pressure wound therapy was applied to closed sternotomy wounds in 57 patients, with a 3% expected SSI rate. No sternal wound infections were seen in any patients. Though this initial report had small numbers of patients, the potential for this low morbidity technique to decrease SSI in sternotomy wounds was seen.

Several reports have investigated the preoperative patient-specific risk factors as well as surgically-related risk factors to predict risk of developing SSI [8]. However, there is no reported study in the medical literature indicating the role or efficacy of either conventional wound care with sterile dressings or the application of V.A.C.® to postoperative abdominal incisions in preventing SSI. However, both methods of wound care are employed on a daily basis in Duke University hospital system (DUMC, Duke Raleigh Hospital and Durham Regional Hospital) as well as other academic and private hospitals across the country. The conventional approach to postoperative surgical wound care has little evidence-based data to support its practice and surgeons have been using incisional V.A.C.® technology for several years in an attempt to curtail SSI in high risk patients.

2.0 NPWT SYSTEMS

2.1 PREVENA INCISION MANAGEMENT SYSTEM

The Prevena Incision Management System (PIMS) is the first battery powered negative pressure product designed specifically for management of closed surgical incisions that continue to drain following sutured or stapled closure. The PIMS covers and protects the incision from external infectious sources, while negative pressure removes fluid and infectious material from the surgical incision.

The Prevena System accomplishes its intended purpose by means of a dressing that seals the area around the incision site. This dressing is fitted with connections for fluid/air lines that provide the means of communication between the wound and the suction apparatus. The pump creates

a negative pressure (vacuum) of -125 mmHg relative to the wound and causes wound exudate to be pumped into the collection canister as necessary.

PIMS consists of:

- a small, portable, battery-powered suction pump,
- a canister for the collection of wound fluids, and
- a sterile, single use dressing kit.

PIMS-associated dressings include either the Peel and Place Dressing or the Customizable Dressing.

The PIMS Peel and Place dressing is an integrated, one-piece dressing comprised of a polyurethane film with acrylic adhesive that provides adhesion of the dressing to the skin surrounding the incision and a polyurethane shell that encapsulates the foam bolster and interface layer, providing a closed system. The polyurethane foam has a pore size of 400-600 microns and a violet colorant. Additionally, the dressing has a built-in pressure indicator, which shows when system pressure is at an acceptable level, and a skin interface layer with 0.019% ionic silver, which wicks fluid from the skin surface. The silver is not intended to treat infection but to reduce potential for contamination of the skin interface layer with microbes. This type of Prevena™ Incision Management System is a 510(k) – cleared, Class II device (K100821).

The Prevena Incision Management System with Customizable Dressing (Prevena Customizable) provides a new dressing configuration that has been designed to allow the clinician to cut the dressing to fit the incision size and geometry. The skin contacting dressing components include:

- a foam bolster with a skin interface layer,
- a hydrocolloid ring that is attached to the foam bolster to assist dressing application and to help reduce dressing leaks,
- hydrocolloid sealing strips for bridging foam dressing pieces, and
- a polyurethane film (V.A.C. Drape).

This product was recently cleared under 510(k) K121883.

PIMS is intended to manage the environment of surgical incisions that continue to drain following sutured or stapled closure by maintaining a closed environment and removing exudate via the application of negative pressure wound therapy. The Prevena System is intended to be applied to the wound site immediately after surgery, and continue for a minimum of 2 days up to a maximum of 7 days, depending on the surgeon's preference.

2.2 ACTIV.A.C. THERAPY UNIT

The ActiV.A.C. therapy unit can be used in special situations in which the incision is larger or has an unusual shape. It is also intended to manage the environment of surgical incisions that continue to drain following sutured or stapled closure by maintaining a closed environment and removing exudates via the application of negative pressure wound therapy. The unit is lightweight and portable to help patients resume their activities of daily living while still receiving the benefits

of V.A.C.® Therapy. The ActiV.A.C. can be used with the Prevena Peel and Place dressing and the Customizable dressing.

The ActiV.A.C unit consists of:

- a small, portable, battery-powered suction pump,
- a canister for the collection of wound fluids,

The ActiV.A.C. is a 510(k) – cleared, Class II device (K120033).

3.0 STUDY RATIONALE

Patients undergoing colorectal (CRS) and hepatopancreatobiliary (HPBS) surgery are at high risk for postoperative complications such SSI and wound dehiscence. Such complications increase the complexity of patient care during recovery from surgery, lengthen post-operative hospitalizations, add significant overall medical costs and may potentially diminish quality of life and economic livelihood. To date, there is no reported study to evaluate the efficacy of either conventional wound care with sterile dressings or the application of V.A.C.® to postoperative abdominal incisions in preventing SSI. Furthermore, there are currently no identifiable additional risks for receiving either conventional wound care or PIMS. Therefore, the proposed study will compare SSI rates for subjects receiving NPWT via PIMS or ActiV.A.C to conventional wound care with sterile dressing.

We hypothesize that incisional NPWT via PIMS or ActiV.A.C.(Kinetic Concepts USA, Inc., San Antonio, TX) compared to conventionally closed laparotomy wounds may decrease the SSI rate in these subject populations which are associated with a high rate of postoperative wound complications.

4.0 STUDY OBJECTIVES

4.1 PRIMARY

- To compare the incidence of SSI rates between conventional wound care versus the incisional NPWT via PIMS or ActiV.A.C. within CRS or HPBS-associated laparotomy wounds as assessed on postoperative day 4-5 and the first postoperative clinic visit.

4.2 SECONDARY

- Characterize the incidence of SSI as superficial incisional, deep incisional, and organ/space as defined by The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) guidelines.

- Assess (or compare) the length of hospital stay between subjects who receive standard of care and incisional NPWT via PIMS or ActiV.A.C.

5.0 STUDY DESIGN

5.1 STUDY DESCRIPTION

This study is a multi-center, open-label, randomized clinical trial conducted at Duke Cancer Institute and Indiana University to evaluate whether incisional NPWT can help reduce the rate of SSI in patients undergoing either colorectal or hepatopancreatobiliary surgery. Up to 170 subjects will be randomized in a 1:1 ratio to either conventional wound care (control group) or the incisional NPWT (experimental group) to ensure 138 evaluable subjects.

The primary study endpoint will be SSI within the laparotomy wound, as assessed on postoperative day 4-5 and the first postoperative clinic visit, which is anticipated to be within 30 days of surgery. Evaluable subjects are defined as those who have been randomized and completed both postoperative assessments. Non-evaluable subjects are those subjects who were randomized but did not complete both post-op visits. Non-evaluable scenarios include aborted surgeries, cancelled surgeries, death unrelated to study, and early device removal related to device malfunction. Screen failures are defined as those subjects not randomized.

Safety endpoints will be adverse events related to the device or dressing, including the presence of any abnormal skin findings (such as blisters or rash). These endpoints will be assessed from the day of surgery through the 30-day follow-up visit.

Subjects randomized to conventional wound care (control group) will have their skin incisions closed with skin staples, sutures, or surgical glue (per judgment of the treating physician), covered with sterile medical gauze and a form of adherent (tape or clear adhesive) for which the subject does not have any allergy. This dressing will be removed per the treating physician's discretion or institutional standards.

Subjects randomized to the incisional NPWT (experimental group) will have their skin incisions closed with skin staples or sutures (per judgment of the treating physician), a layer of non-adhesive dressing (Adaptic: Johnson & Johnson, New Brunswick, New Jersey) will cover the skin staples or sutures, followed by placement of an adhesive (Benzoin: generic), a Prevena™ Incision Management System peel and place or customizable dressing (KCI USA, Inc, San Antonio, Texas) covering only the skin staples or sutures. Please note, surgical glue should not be used for the experimental group. NPWT will be delivered using either the Prevena pump or the ActiV.AC. The incisional NPWT will then be continued for a minimum of 2 days up to a maximum of 7 days depending on physician preference.

Subjects will be clinically managed according to routine standard of care. Subjects will be assessed during their inpatient stay and at the time of routine postoperative clinic visits which is anticipated to be within 30 days of discharge. Presence or absence of SSI will be determined on postoperative day 4-5 and again at the time of the postoperative clinic visit, which is anticipated to be within 30 days of discharge. Criteria for determination of SSI are listed in Section 8.

Patients who are candidates for a laparoscopic approach will not be recruited. Note: patients scheduled for a staging laparoscopy followed by an open procedure are permitted to participate.

See Appendix 1 for the study schema.

5.2 RANDOMIZATION

Subjects who meet all inclusion criteria and no exclusion criteria and who consent to participate in the study will be randomized in a 1:1 ratio to receive either incisional NPWT via PIMS or ActiV.A.C or the standard-of care dressing following surgery. Randomization may occur up to 5 business days prior to surgery. If a subject is randomized and surgery is subsequently delayed, they will not be re-randomized even if outside the 5-day window.

Randomization will be stratified according to surgical site (colorectal vs hepatopancreatobiliary) and body mass index (BMI), < 30 vs ≥ 30.

Randomization using permuted block scheme will be done via REDCap Randomization Application. Please refer to the randomization manual for detailed instructions.

6.0 SUBJECT SELECTION

6.1 INCLUSION CRITERIA

1. Female and male patients 18 years of age or older
2. Scheduled for an elective surgery in either open CRS or open HPBS. This includes, but is not limited to: ileocecectomy, right hemicolectomy, extended right hemicolectomy, transverse colectomy, left hemicolectomy, sigmoidectomy, proctectomy, low anterior resection or abdominoperineal resection, hepatectomy, bile duct reconstruction, duodenectomy, pancreatectomy, pancreaticoduodenectomy, or pancreatic duct reconstruction

6.2 EXCLUSION CRITERIA

1. The need for emergency surgery.
2. The need for use of only laparoscopic surgery. Note: Hand-assisted laparoscopic procedures are not exclusionary. Patients scheduled for a staging laparoscopy followed by an open procedure are permitted to participate.
3. Presence of bowel obstruction, strangulation, peritonitis or perforation.
4. The presence of local or systemic infection preoperatively.
5. ASA class ≥4.
6. Inability to provide informed consent and authorization.
7. Known allergy or hypersensitivity to silver.
8. Patients who are pregnant
9. Any clinically significant condition that, in the investigator's opinion, would significantly impair the subject's ability to comply with the study.

6.3 INCLUSION OF WOMEN AND MINORITIES

Men and women of all races and ethnic groups are eligible for this trial.

7.0 STUDY ASSESSMENTS

7.1 STUDY CALENDAR

	Baseline[a]	Cycle Day		
		Day of Surgery	Post-op Visit 4-5 days	Post-op Visit 30 days (+/-14)
Informed Consent	X			
Demographics	X			
Medical and Surgical history	X			
Physical Exam and Vital Signs	X			
Pregnancy Test[b]	X			
Randomization[c]		X		
Incisional NPWT via PIMS or ActiV.A.C or standard wound application[d]		X		
Incision Assessment			X	X
Adverse Event Assessment		Throughout Study		
Concomitant Medication	X			

a: Screening procedures will be performed within 42 days prior to surgery.
b: Serum or urine pregnancy test in women of childbearing potential will be performed within 30 days prior to surgery
c: Randomization may occur within 5 business days of surgery.
d: Wound application will be done in the operating room by the OR team.

7.2 SCREENING AND BASELINE EVALUATIONS

All baseline assessments must be done within 42 days of surgery.

- Physical Exam and vital signs
- Medical History
- Surgical History
- Concomitant Medications (must be done or confirmed on the day of surgery): Include a list of pre-treatment chemotherapy and/or radiation for rectal cancer patients. Also include antibiotics within 30 days prior to surgery, steroid use within 1 week prior to surgery, medications related to anticoagulation within 30 days prior to surgery.

A serum or urine pregnancy test will be conducted on women of childbearing age within 30 days prior to surgery.

Eligibility will be reviewed by two key personnel prior to randomization to ensure eligibility (inclusion and exclusion) criteria have been met. The PI will review final eligibility prior to surgery.

7.3 EVALUATIONS DURING STUDY

7.3.1 Throughout Study

- Adverse Event evaluation specific only to the NPWT units and dressings unit (e.g. blistering, redness)

7.3.2 Day of Surgery

- Randomization (or within 5 business days of surgery)
- NPWT via PIMS or ActiV.A.C. or standard of care wound application; application will be done in the operating room by the OR team.

7.3.3 Post-op Visit Day 4-5

- Post-operative incision assessment
- Review of any side effects or symptoms
- This may be conducted by a review of clinical data
- PI will confirm the clinical data of any finding indicative of infection (i.e. redness, fever, positive culture)

7.3.4 Post-op Visit Day 30 (+/-14)

- Post-operative incision assessment
- Review of any side effects or symptoms
- This may be conducted by a review of clinical data

- PI will confirm the clinical data of any finding indicative of infection (i.e. redness, fever, positive culture)

8.0 CLASSIFICATION OF SSI BY NSQIP

The following definitions will be used to classify SSI:

Superficial Incisional SSI: Superficial incisional SSI is an infection that occurs within 30 days after the operation *and* infection involves only skin or subcutaneous tissue of the incision *and* at least *one* of the following:

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

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

- Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
- 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.
- An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
- Diagnosis of a deep incision SSI by a surgeon or attending physician.
- Report infection that involves both superficial and deep incision sites as deep incisional SSI.

Organ/Space SSI: Organ/Space SSI is an infection that occurs within 30 days after the operation and the infection appears to be related to the operation *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:

- Purulent drainage from a drain that is placed through a stab wound into the organ/space.
- Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
- An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.

- Diagnosis of an organ/space SSI by a surgeon or attending physician.

Do not report the following conditions as SSI:

- Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).
- Infected burn wound.

9.0 SUBJECT DISCONTINUATION

Subjects may withdraw from this study at any time.

Reason for discontinuation from the trial will be recorded.

The Principal Investigator may discontinue a subject from the protocol regimen. Reasons for subject discontinuation by the investigator may include but are not limited to the following:

- Death
- Investigator or PI determination that it is not in the subject's best interest to continue participation
- Lost to follow-up

10.0 STATISTICAL METHODS

Administrative Summary
Between July 2016 and June 2017, institutional SSI rates were 29% and 9% for Whipple procedures and liver resections, respectively. Based on these lower than expected SSI rates we decided to compute the observed, overall infection rate among patients currently enrolled and treated on this trial to assess whether the trial hypotheses were reasonable assumptions. The current overall infection rate was estimated to be 11%. In addition, the observed percent of ineligible/non-evaluable patients was 14%. Consequently, the null and alternative hypotheses of the present trial are being amended from the previous null and alternative hypotheses of 30% and 15%, respectively to 17% and 5%, respectively, to reflect the overall, observed infection rate. The revised, maximum sample size will be inflated to reflect the observed percent of inevaluable patients, 14%. As of February 2018, 131 patients were randomized; no statistical analysis of the study endpoint has been conducted to date.

Revised Statistical Considerations
The primary study endpoint is SSI rate. Patients will be stratified by surgical site (colorectal vs hepatopancreatobiliary) and BMI (<30 vs ≥30), and randomly assigned to conventional wound care group or negative wound pressure group with 1:1 allocation. The hypothesized SSI rate is 17% for the conventional wound care group (control group) [1]. We anticipate a reduction of the rate to 5% in the negative wound pressure group (experimental group).

As this is a phase II study, a larger type I error rate of 0.1 will be used. Based on a chi-square test comparing two-sample binomial probabilities at a 1-sided significance level of 0.1, the study has approximately 85% power to detect the difference in SSI rates between 17% in the control

group and 5% in the experimental group. With the allowance of 14% ineligible/non-evaluable patients (based on the observed percentage of evaluable patients to date), up to 170 patients (85 per arm) will be enrolled. Given that 143 patients have already enrolled on the study, up to 27 additional patients will be accrued to meet the revised, maximum study sample size.

With an accrual rate of 4 patients per month, we expect to complete the additional accrual in less than 8 months.

Preoperative, intraoperative, and postoperative variables will be prospectively collected.

10.1 STATISTICAL ANALYSIS

The primary analysis will include all randomized and evaluable patients but exclude ineligible patients or patients who are canceled from the study before receiving any wound care. SSI is defined as an infection that occurs within 30 days of operation. The primary endpoint is the SSI rate. The primary analysis of comparing the conventional wound care (control group) and the incisional V.A.C® (experimental group) will be conducted using a chi-square test for two-sample binomial probabilities with a one-sided significance level of 0.1. The observed SSI rates and 90% Upper Confidence Bound (UCB) estimates will be reported. Preoperative, intraoperative, and postoperative variables will be tabulated and appropriate summary statistics will be reported. As a secondary analysis, comparison of treatment groups for SSI will be adjusted for any significant preoperative, intraoperative, or postoperative variables using logistic regression.

For secondary endpoints, the incidence of SSI as superficial incisional, deep incisional, and organ/space will be estimated along with the 90% UCBs. The secondary endpoint length of stay is a continuous variable. A Wilcoxon rank sum test will be used to assess the significance of the difference between groups in median length of stay. Median length of stay, its range and quartiles will be reported.

11.0 INVESTIGATIONAL PRODUCT

The PIMS and ActiV.A.C. therapy units and associated dressings will be supplied by KCI.

Incisional NPWT will be removed prior to hospital discharge.

In the event that the clinician or study designee encounters issues with PIMS or control dressings prior to the desired time for removal, dressing replacement/reinforcement is acceptable but must be documented in the case report form (CRF). The PIMS unit may also be switched to use an ActiV.A.C unit. Any loss of negative pressure will be documented and will not determine subject evaluability. Please refer to the PIMS Instructions manual for guidance on operational questions.

A PIMS canister filled with 45 mL of wound fluid will lead to a “canister full” alarm.

11.1 INVESTIGATIONAL PRODUCT STORAGE AND ACCOUNTABILITY

The PIMS and ActiV.A.C. therapy units and associated dressings are to be stored in a secure, limited-access location with ambient room temperature away from direct sun exposure and moisture.

No investigational product will be released until the KCI receives written confirmation that the IRB has approved the clinical study.
Prior to the release of product to the site, the funding source, KCI shall complete the appropriate Investigational Product Release and Inventory Control Forms, which will accompany the shipment of the investigative product and serve as a shipping record from the funding source.

Upon receipt of product, the Principal Investigator (PI), or designee, will inventory the shipment and verify the lot numbers (PIMS) and serial numbers (ActiV.A.C units) against the information provided on the Investigational Product Release Form. The PI, or designee, will sign the form and return it to the funding source, or designee, with notations regarding any missing investigational product or other discrepancies.

The PIMS and ActiV.A.C. therapy units and associated dressings that are not dispensed for the study will be returned to KCI at the end of the study.

12.0 SAFETY REPORTING REQUIREMENTS

12.1 DEFINITIONS

The definitions in this section have been adapted from the Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practices (GCPs). Please refer to the complete regulations and guidelines for additional details regarding these definitions. This study will only evaluate adverse events that are probably or possibly related to the NPWT units and dressings (e.g. blistering, redness, etc).

Adverse Event (AE) [ICH GCP]: An Adverse Event (AE) shall mean any untoward medical occurrence. For the purposes of this study, only adverse events thought to be related to the dressing will be collected and recorded.

Unanticipated adverse device effects [21 CFR 812.150]: Any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

Deviations from the investigational plan [21 CFR 812.150]: An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety or welfare of human subject, FDA and IRB approval is also required.

12.2 PROCEDURES FOR REPORTING

All adverse events deemed possibly or probably related to the NPWT unit and dressings that are identified from the time of placement of the NPWT or standard of care wound application through 30 days post-surgery should be recorded on the CRFs.

Serious Adverse Events (SAEs) must ALSO be reported within 2 business days of learning of an event. The DCI Safety SAE Review Form must be completed and promptly submitted to the funding company. The forms should include at minimum the following information but should not be held until all information is available. The funding source, KCI, will be notified using the KCI USA, Inc. SAE Report Form. The Duke study team will send SAE Report Form to KCI USA, Inc. within 2 business days of knowledge of the SAE. External sites should report SAEs to the Duke study team within 24 hours. Reporting instructions for external sites can be found in the REDCap study eManual. The Duke study team will be responsible for reporting to the supporting company as well as the Duke IRB and/or FDA, where applicable. In accordance with applicable regulations, Investigators must report SAEs to their local IRB according to their institutional guidelines.

Additional information and/or corrections may be submitted as they are obtained. All SAEs must be followed through resolution or stabilization.

The initial report for each SAE should include <u>at minimum the following information:</u>

- protocol # and title
- patient initials, study identification number, sex, age
- date the event occurred
- description of the SAE
- description of the patient's condition
- indication whether the patient remains on study
- causality or causal relationship

SAEs should be reported by fax to the following:

KCI USA, INC
Fax: 1-800-275-4290
Email: SAE@kci1.com

Events will be reviewed and reported to the Duke IRB according to local IRB guidelines.

13.0 DATA AND SAFETY MONITORING

13.1 MONITORING

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team

will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1 – 3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Cancer Protocol Committee, the Safety Oversight Committee (SOC), the funding source, the Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team, the Duke School of Medicine Office of Regulatory Affairs and Quality (ORAQ) and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

13.2 SAFETY OVERSIGHT COMMITTEE

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews include but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team oversees the conduct of DUHS cancer-related, sponsor-investigator therapeutic intervention and prevention intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

13.3 SUBJECT CONFIDENTIALITY

In order to maintain subject privacy, all case report forms (CRFs), study drug accountability records, study reports, and communications will identify the subjects by initials or the assigned subject number. The investigator will grant monitor(s) and auditor(s) from the funding source, or designee and regulatory authority(ies) access to subject original medical records for verification of data gathered on the CRFs and to monitor/audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

13.4 INVESTIGATOR COMPLIANCE

The investigator will conduct the study in compliance with the protocol provided by the sponsor and funding source and will obtain approval by the IRB and appropriate regulatory authority(ies). Modifications to the protocol should not be made without agreement of the investigator and funding source. Changes to the protocol will require written IRB approval prior to the implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. If applicable regulatory authority(ies) permit, the IRB may provide expedited review and approval for minor changes in ongoing studies that have the approval of the IRB. Sponsor or designee will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the investigator will contact the funding source or designee, if circumstances permit, to discuss the planned course of action. All departures from the protocol must be fully documented.

13.5 AUDITS

The Duke School of Medicine Office of Regulatory Affairs and Quality (ORAQ) may conduct audits to evaluate compliance with the protocol and the principles of GCP. The PI agrees to allow the ORAQ auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the ORAQ auditor(s) in order to discuss findings and any relevant issues.

ORAQ audits are designed to protect the rights and well-being of human research subjects. ORAQ audits may be routine or directed (for cause). Routine audits are selected based upon risk metrics generally geared towards high subject enrollment, studies with limited oversight or monitoring, Investigator initiated Investigational Drugs or Devices, federally-funded studies, high degree of risk (based upon adverse events, type of study, or vulnerable populations), Phase I studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.

ORAQ audits examine research studies/clinical trials methodology, processes and systems to assess whether the research is conducted according to the protocol approved by the DUHS IRB. The primary purpose of the audit/review is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit/review will serve as a quality assurance measure, internal to the institution. Additional goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize “best practices” in the research/clinical trials environment.

14.0 DATA MANAGEMENT AND PROCESSING

A Medidata Rave database will be the data collection tool for the study.

An audit trail is maintained automatically by the electronic CRF management system. All users of this system will complete user training.

14.1 STUDY DOCUMENTATION

Study documentation includes but is not limited to source documents, case report forms, monitoring logs, appointment schedules, study team correspondence with sponsors, funding source or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated “Regulatory Binder”, which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or

transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

15.0 ADMINISTRATIVE SECTION

15.1 REGULATORY AND ETHICAL COMPLIANCE

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

15.2 DUHS INSTITUTIONAL REVIEW BOARD AND DCI CANCER PROTOCOL COMMITTEE

The protocol, informed consent form and pertinent protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

15.3 INFORMED CONSENT

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent

form will be provided to the subject. The Principal Investigator is responsible for asking the subject whether the subject wishes to notify his/her primary care physician about participation in the study. If the subject agrees to such notification, the Principal Investigator will inform the subject's primary care physician about the subject's participation in the clinical study.

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

15.4 PRIVACY, CONFIDENTIALITY, AND DATA STORAGE

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained.

Upon completion of the study, research records will be archived and handled per DUHS HRPP policy.

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

15.5 STUDY CLOSURE

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness

16.0 REFERENCES

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APPENDIX 1 STUDY SCHEMA