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PROTOCOL

PROSPECTIVE EVALUATION OF WOUND MANAGEMENT USING VACUUM ASSISTED INSTILLATION THERAPY IN EMERGENT CONTAMINATED ABDOMINAL SURGERIES

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Sample Size: 20 subjects

Introduction:

Postoperative surgical site infection (SSI) remains a common and serious complication after emergency abdominal surgery with incidence varying between 14 to 32% (1, 2). Seamon et al in a study of 503 trauma patients who underwent laparotomies for *any* enteric injuries demonstrated that primary closure leads to a 3 fold increase in SSI rate (32.1% vs. 9.8%) and 3 fold increase in fascial dehiscence (8.6% vs. 2.6%) compared to wounds managed with delayed closure (3). In contrast, an individual undergoing major *elective* operation is expected to have a 2% risk of SSI (4).Among the various gastrointestinal sites, colorectal procedures are associate with the highest risk of SSI due to the change in bacterial flora from largely aerobic gram-positive organisms in the proximal bowel to more virulent anaerobic species in the colon and rectum such as Escherichia coli, Streptococcus, Bacteroides fragilis, Proteus and Klebsiella (5-8).In a prospective cohort study of 2393 patients undergoing elective colorectal surgeries, Huebner et al. has shown hospital SSI rates varying between 4% to 25.2% and individual surgeon rates varying from 3.7 to 36.1% (9-14). The most feared consequence of SSI is fascial dehiscence and necrotizing soft tissue infections, which can lead to some of the most difficult surgical complications such as large ventral hernias or enterocutaneous fistulas (15-17).

Over the years, various techniques have been employed to decrease SSI after bowel surgeries, particularly in emergent cases with significant enteric contamination. They include wet –to-dry dressing changes followed by delayed primary closure; wet-to-dry for several days, followed by VAC; or take a chance with infection with primary closure. Unfortunately, in the current age of medical practice treatment of the abdominal wound after emergent surgeries with enteric contamination is still largely "surgeon preference." Among the previously mentioned techniques, most employ some form of wet-to-dry dressing change (18-19). A systematic review of 8 clinical trials encompassing 623 patients with contaminated abdominal wounds randomized to wet-to-dry dressings or delayed primary closure did not provide definitive evidence that there is advantage of one over the other in reducing surgical site infections (20). Either method involves the patient having an open wound for some time that is resource intensive and costly to manage, not to mention traumatic for the patient (21).

The VAC has revolutionized the management of complicated wounds. It operates on the principles of applying constant negative pressure therapy to a wound bed through a porous sponge to stimulate local blood flow, decrease interstitial edema and remove harmful enzymes in order to promote healing (22-25). However, the immediate application of the VAC after emergent highly contaminated operations has not been studied. Anecdotally, surgeons are reluctant to immediately use the VAC because theoretically the local environment after VAC closure is similar to primary closure. Some surgeons, however, will use the VAC after an initial 3 to 4 days of wet-to-dry, when the wound is heavily infiltrated with host neutrophil activity. This is a common approach at our institution. However, patients without insurance coverage cannot benefit from this technique, and often have to resort to the cumbersome and painful wet-to-dry dressing changes. A technique utilizing existing technology that can achieve definitive wound closure before the patient is discharged home is desperately needed. The VeraFlo, we believe, is that solution.

The Vacuum-Assisted Closure (V.A.C.) VeraFlo System (Kinetic Concepts, Inc., San Antonio, TX) combines the original VAC with a fluid infusion system into the wound bed. A calculated amount of bactericidal solutions such as Dakin's solution can be infused into a contaminated wound, bath the wound for predetermined intervals, then removed via the proven mechanics of the VAC system. The VAC system has been shown to be suitable for complicated wounds resulting from trauma and infection (22-27). It has also been theorized that contrary to the wet-to-dry technique, VAC instillation therapy allows distribution of the irrigant evenly over the entire wound bed. Various solutions have been utilized for infusion, including Normal Saline and Dakin's Solution up to ¼ strength.

Dakin's solution, or sodium hypochlorite (NaOCl), has been shown to be bactericidal to organisms commonly associated with surgical wound infections such as Enterococcus species, Bacteroides fragilis, and E. coli. 0.125% Dakin's solution is commonly used for daily wet-to-dry dressing changes in chronic wounds (28-29). Exposure of the above mentioned virulent bacterial cultures inoculated onto agar plates for 30 minutes at the standard concentration of 0.25% and 0.025% of Dakin's solution proved it to be bactericidal against all organisms. Additionally, animal studies showed no difference between the Dakin's solution at this dilution and Normal Saline controls in *in vivo* toxicity on fibroblasts. The concern of using the VAC immediately on highly contaminated wounds due to bacterial proliferation is now mitigated by the addition of the bactericidal instillation therapy.

We propose using the VeraFlo with Dakin's solution for the first 3 postoperative days, followed by delayed primary closure on postoperative day 4. We believe this technique can achieve earlier wound closure, decrease patient discomfort, improve cost savings, and potentially standardize and revolutionize our management of heavily contaminated wounds.

Clinical Hypotheses:

We hypothesize that immediately after emergent operations involving enteric injuries e.g. traumatic injuries involving stomach, small bowel, or colon; or the non-trauma emergent general surgical pathologies involving the above hollow viscera, the application of VeraFlo with ¼% Dakin's solution for 3 days, followed by delayed primary closure on postoperative day 4, will be associated with a low risk of wound infection, achieve more expedient wound closure, ease nursing care and increase patient comfort compared to the current common practice of wet-to-dry dressing changes.

Primary Outcome:

The primary outcome of the study will be the rate of superficial and deep incisional surgical site infection, as defined by the Center for Disease Control and Prevention (CDC) definitions. (30).

Superficial incisional SSI
Must meet the following criteria:
Infection occurs within 30 days after any NHSN operative procedure (where day 1 = the procedure date), including those coded as 'OTH'*****
a*nd*
involves only skin and subcutaneous tissue of the incision
and
patient has at least one of the following:
a. purulent drainage from the superficial incision.
b. organisms isolated from an aseptically-obtained culture of fluid or tissue from the superficial incision.
c. superficial incision that is deliberately opened by a surgeon, attending physician or other designee and is culture positive or not cultured
and
patient has at least one of the following signs or symptoms: pain or tenderness; localized swelling; redness; or heat. A culture negative finding does not meet this criterion.
d. diagnosis of a superficial incisional SSI by the surgeon or attending physician or other designee .

Deep incisional SSI
Must meet the following criteria:

Infection occurs within 30 or 90 days after the NHSN operative procedure (where day 1 = the procedure date)
and
involves deep soft tissues of the incision (e.g., fascial and muscle layers)
and
patient has at least one of the following:
a. purulent drainage from the deep incision.
b. a deep incision that spontaneously dehisces or is deliberately opened by a surgeon, attending physician** or other designee and is culture-positive or not cultured
and
patient has at least one of the following signs or symptoms: fever (>38°C); localized pain or tenderness. A culture-negative finding does not meet this criterion.
c. an abscess or other evidence of infection involving the deep incision that is detected on direct examination, during invasive procedure, or by histopathologic examination or imaging test.

A. **Secondary Efficacy Endpoint(s):**

1. Time to complete wound closure
2. Cost analysis: Cost-effectiveness ratio is determined by the net cost of material supplies, human labor, and the health effect of an intervention. The net cost includes the direct cost of drug, the equipment and their administration, and also on any savings that might be achieved by using this method, such as reduction in hospital stay, decrease of antibiotic usage.
3. Pain score as defined by the Wong-Baker Pain Scale related to the VeraFlo presence/manipulation.

B. **Safety Endpoint(s):** wound infection and adverse reaction to Dakin's Solution.

Design:

A. □ Basic Science (Bench or Laboratory) □Pre-Clinical (Animal) □ Clinical (Human) X
B. □ Care Report □ Registry □ Study (Trial) X
C. □ Retrospective □ Prospective X
D. □ Non-randomized X □ Randomized
E. □ No Control or Sham □ Sham-controlled □ Reference-controlled X
F. □ Single-arm X □ Multiple-arms - Specify (#): ____
G. □ Single-center X □ Multiple-centers - Specify (#): ____

Study Intervention and Duration:

A. Retrospective Study: Start Date _____ End Date_____
B. Date First Patient (FPI) or Subject (FSI) In: September 22, 2014
C. Date Last Patient (LPO) or Subject (LSO) Out: September 22, 2015
D. Total Duration: 1 year to allow time for patient recruitment, quality assurance and analysis. Subjects will be followed from admission to their two-week post-operative clinic visit.

Study Population:

This is a prospective cohort study that will be performed at the University of Arizona Medical Center (UAMC), a Level I Trauma center. Patients who undergo emergent surgery for trauma induced enteric injuries

involving the stomach, small bowel, or colon (ex: gun-shot wounds, stab wounds, blunt colon perforation) or the non-traumatic emergent general surgical pathologies involving the above hollow viscera.

Retrospective review of our database over the past 3 years identified total of 276 patients: 157 patients underwent emergent surgery for trauma related colon injuries and 43 patients due to acute perforated diverticulitis. In addition, 76 patients underwent emergent abdominal surgery for perforated viscus excluding colonic pathologies. Based on these results, we conservatively estimate an average of 90 patients per year will require emergent abdominal surgery for perforated viscus. Thus, we anticipate **enrolling 20 patients** over the 1 year period. This will be followed by data collection, follow-up period, data analysis and report/manuscript about research findings.

Subject Inclusion Criteria:
Patients 18 years and older
Emergent surgeries involving enteric injuries e.g. traumatic injuries involving stomach, small bowel, or colon; or the non-trauma emergent general surgical pathologies involving the above hollow viscera.

Subject Exclusion Criteria
Prisoners
Age<18
Pregnancy
Patients with allergy to Dakin's (sodium hypochlorite) solution
Enrolled in a concurrent ongoing interventional, randomized clinical trial.

This prospectively collected cohort of patients will be compared to the similar historical cohort from 2008-2013. We will review medical charts of the patients admitted to UAMC following the same inclusion and exclusion criteria described above to perform a retrospective review. We will collect the same data points as in prospective cohort.

Resources available to conduct the Human Research:

The study will be conducted at UAMC with the support from the Division of Trauma, Critical Care, and Emergency Surgery. We have a dedicated research team to support this project which includes a research coordinator, four research fellows, 24/7 coverage by research nurses and 2 research assistants trained to conduct human research studies, as well as support from the trauma surgeons to identify eligible patients. Patients will be consented by the PI, other trauma attending surgeons, research coordinator or the research fellows, who all have been fully trained in human research.

Recruitment Methods and Consenting Process:

The attending trauma surgeon will identify eligible patients for the prospective cohort. Recruitment and consent will happen in person with a thorough explanation of the treatment protocol by the PI, trauma surgeons, research coordinator or a research fellow. Patients or their Legal Authorized Representatives (LAR) will be informed about the study and consented. Should the patient or the LAR decline participation in the study, immediate cessation of data collection will take place and their information will not be included in the final data analysis.

Retrospective cohort of patients will be identified through medical chart review and we request waiver of consent for this patient population under 45 CFR 46.116(d) and 21 CFR 50.55 (d) as this retrospective research involves no more than minimal risk to subjects, doesn't alter the treatment or management in anyway as it had

already been completed, and it could not practicably be carried out without the waiver as those patients have completed their treatment and it would be extremely hard to obtain consent.

Procedures Involved in the Human Research:

We will approach patients upon the diagnosis to consent them for this prospective study. During the process, the details of the trial will be reviewed along with potential risks and benefits, the endpoints of interest and the process by which these endpoints are evaluated. When notified of trial enrollment, the patient or their legal representative will be given the opportunity to withdraw from further data and sample collection. Those who consent will be enrolled to collect data on outcomes, baseline parameters and follow-up period to evaluate efficacy of VeraFlo for management of contaminated abdominal wounds after emergent surgery. VAC with ¼% Dakin's solution will be placed immediately at the end of the surgery for the first 3 postoperative days, followed by delayed primary closure on postoperative day 4. Wound will be swabbed at the end of surgery before placing the VAC and before skin closure on Day 4. All follow-ups will be performed as a standard of care.

Data collected will include the following: demographics (i.e. BMI), hemodynamic parameters at the time of presentation and operation, source of infection, imaging studies outcomes, lab tests, surgical procedure performed and its duration, vasopressors, estimated blood loss and transfusion records, antibiotics used and duration, comorbidities (Charlson Morbidity Index, APACHE II), trauma registry data, and complications (if any) during their hospital stay and follow-up in clinic, length of stay (in ICU and in hospital), intra-abdominal wound culture, wound closure details, pain level, cost, wound appearance (recorded by photograph), wound culture, infection, time of nursing care.

Specific Study and/or Reference Product(s) Treatment Protocol(s):

Risks to Subjects:

This protocol involves minimal risk. Currently, use of VAC therapy to manage contaminated abdominal wounds is an accepted practice. Dakin's solution has been commonly used in clinical practice in wet-to-dry dressing changes. This protocol, which involves the delivery of ¼% Dakin's solution through the VAC VeraFlo to contaminated abdominal wounds, will formally establish the safety and efficacy of this technique. In addition, this protocol involves microbiological wound culture which is routinely done to patients with contaminated wounds. The risk of the proposed protocol is the same as clinical care.

Serious Adverse Events:

Serious Adverse Events/KCI USA, Inc. Reporting Information

Notification of the event will occur via the KCI USA, Inc. SAE Report Form. This form should be completed by the investigator, or designee, and faxed to KCI USA, Inc. Initial notification of the event may occur via telephone call to a KCI study contact, but must always be followed by written notification using the SAE Report Form by the close of the next business day. The KCI USA, Inc. SAE fax line is available for SAE reporting 24 hours per day and is monitored during normal business hours.

KCI USA, INC. SAE REPORTING BY FAX
Investigation: Insert Protocol Name Here
Fax Number: 1.800.275.4290

Statistical Analysis:

Sample Size Calculation:

A. Event Rate Assumption(s): <5%
B. Study Group (%):100%
C. □ Comparator or □ Sham Group (%): historic cohort from previous 3 years.
D. Power Estimation: □ 95% □ 90% 85% □ 80% or Other – Specify: ___%
E. Evaluable Rate Consideration: Specify: ___%
F. Sample Size Calculation: _20___ Total Number of Subjects. When population is not divided evenly, please specify how it will be divided and rationale for doing so:

G. Interim Analysis - Sample Size Re-calculation: □ Yes □ No X Specify rationale:

H. Number of Centers Projected: _1___

This is an observational prospective study with no concurrent arm for comparison; we will use historic data from our center over the last 3 years to analyze results. The advantage of this approach is that there was no change in medical providers among trauma surgeons in the last 3 years. We also have a robust prospectively collected trauma registry that allows performing this analysis. We will identify patients who have undergone emergent abdominal surgery with hollow viscus violations, and had undergone wet-to-dry dressing changes. A Propensity matching analysis will be performed to match patients from the historic cohort to the current patients by demographics, disease severity and laboratory tests. A univariate analysis, independent t-test, and a Kaplan-Meier survival analysis will be performed to compare rate of infection, time-to-closure, and cost analysis.

Potential Benefits to Subjects and/or Society:

Current literature shows strong independent benefits of using Dakin's solution and the negative pressure VAC therapy for managing open contaminated wounds. The solution and the device have also been shown not to be harmful. Currently, there is no standard management protocol regarding the combined utilization of Dakin's solution with VAC therapy, a capability delivered by the KCI VeraFlo. This study aims to study the utility and safety of using the VeraFlo with ¼% Dakin's solution in managing contaminated abdominal wounds. If it is associated with less SSI and earlier achievement of wound closure, then this technique may serve to standardize the management of contaminated abdominal wounds. It has the potential to decrease the time and resource spent on managing open abdominal wounds as compared to the most common technique of wet-to-dry dressing changes. In addition, this technique has the potential to drastically improve patient comfort, convenience and satisfaction.

Provisions to Protect the Privacy of Subjects and the Confidentiality of Data:

All research activities take place within the clinical setting that standard of care is rendered. Stringent application of all federal, state, and institutional regulations and policies pertaining to patient privacy will be inherited within these activities. Patients or LAR will be consented in a private area according to HIPPA regulations. All research staff has undergone HIPPA compliant training. Staff functioning within the clinical areas has experience as clinical providers as well, making them well suited to implement this particular research study. All data collected will be kept in the secured office and stored on the password-protected computers at the COM domain for 6 years after conclusion of research.

Access to Private Information:

Authorization for access to Protected Health Information (PHI)

We will obtain authorization from prospectively recruited subjects to access medical record information for research purposes and PHI will be added to the main consent.

For control cohort:
Waiver for Authorization for Access to Protected Health Information and Waiver of Consent:

We are requesting a waiver of specific consent and PHI authorization for the retrospective cohort of this study as under 45 CFR 46.116(d) and 45 CFR 164.512 (i)2(ii). The research involves no more than minimal risk to the subjects as it is retrospective in nature and patients' treatment has been already completed. We will be instituting specific safeguards for protection of this information. It is highly unlikely that a breach of PHI will occur, and this waiver will not adversely affect the rights and welfare of the subjects. As this is a retrospective review of data from the UAMC, it would be difficult to carry out this research without the waivers. All data will be kept under password protected account on the Department of Surgery computer. Deidentified SAE's will be shared with KCI. Records will be kept for 6 years in room 5411 in electronic format and destroyed thereafter. The population in question has already received medical treatment, so there will be no possible impact on their overall medical care access or treatment.

As there is no physical, verbal, or written contact with the subjects who have already received medical treatment, there is little to no risk of physical emotional, social, or economic harm. All reasonable steps will be taken to minimize the information to the minimal amount needed for the study.

Cost to Subjects:

There should be no additional cost to the subjects involved. Subjects will have no additional costs for participating in the study. Subjects, or their 3rd party payer, will be responsible for all standard-of-care charges that are routinely given to patients. Subjects will not be charged for VAC device or Dakin's solution as well as microbiological analysis specifically performed for research purposes.

Subject Compensation:

No compensation will be provided to subjects.

Medical Care and Compensation for Injury:

Medical care for AE/SAE's is immediately available during the inpatient duration. No funds for care or injury compensation have been set aside. Costs incurred remain the responsibility of the patient and/or responsible party.

Monitoring the Data for Subject Safety:

This protocol has only minimal risk to subjects and carries the same risks as a standard clinical care. Hence, there is no need for data monitoring committee.

Withdrawal of Subjects:

Patients will have an option to withdraw from the study at any point of time without risk. All data collection will be stopped at that point. Collected microbiological cultures and data obtained up to that point will be used for research, but no further samples or data will be obtained.

The patient or their LAR will have the option of withdrawing from the study.

If abrupt withdrawal is necessary a patient will not be placed at risk. Their care will continue to be of the highest quality following current standards of care. If a patient withdraws from the project they will not continue to participate in this project and further data collection will cease. All research data collected up to the point of withdrawal will be obtained and analyzed.

Sharing of Results with Subjects:

There is no intent to share study results with the respective subjects. If a particular need arises to address unique findings regarding a particular subject, it will be handled on a case by case basis. De-identified results will be published in scholarly journals at the completion of the study. This data will be available to the general public.

Information Management:

We will not be distributing specimens to collaborating entities. The subjects will be identified by a study number only. All hard copy source documentation will be kept in a secured, locked cabinet in the site's research coordinator's office. All study documents will be maintained in a secure location per university policy, currently six years after conclusion of study. The following data will be collected from each patient: demographics (i.e. BMI), hemodynamic status at the time of presentation and operation, procedure performed and its duration, vasopressors, estimated blood loss and transfusion records, antibiotics used and duration, comorbidities (Charlson score, APACHE II), complications (if any), length of stay (in ICU and in hospital), intra-abdominal wound culture, wound closure details, pain level, cost, wound appearance (recorded by photograph), wound culture, infection, time of nursing care.

The electronic data will be entered and maintained on password protected computers stored in the investigator's office. All the data will be destroyed following the minimum 6 year requirement period by shredding any remaining documents and/or deleting computer files with linking information so there is no direct link to subject identifiers and information.

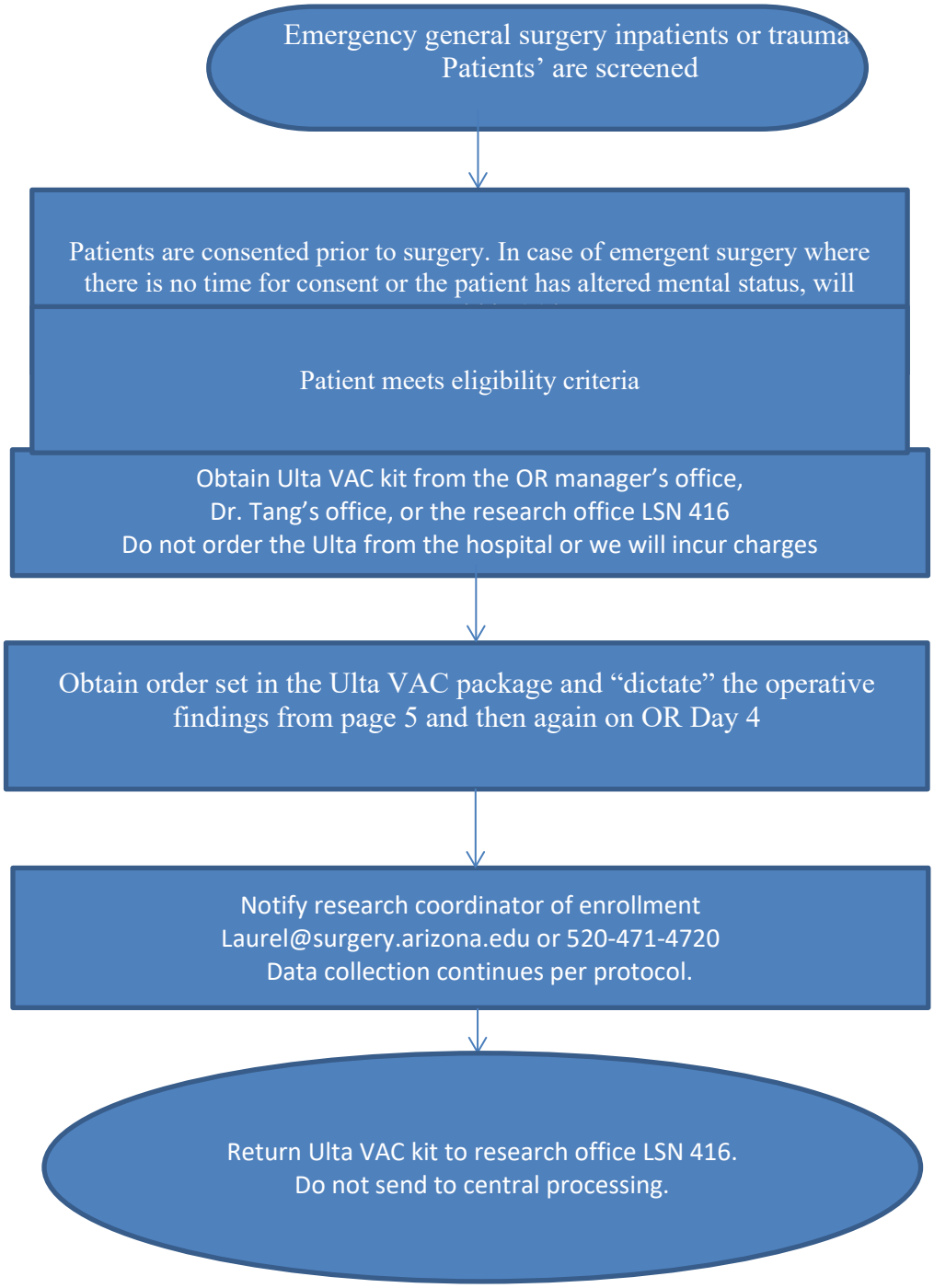
Drugs, Devices, and Gases:

V.A.C.Ulta™ Negative Pressure Wound Therapy System is a 510(k) –cleared, Class II device (K100657) is the device manufactured by KCI and designed to provide a negative-pressure wound therapy. VeraFlo therapy prevents further wound contamination, manage excess exudates, optimize wound bed, cleanse the wound and provide antimicrobial antiseptic treatment. Combined with appropriate wound solutions it may help control the bacteria known to form biofilm. ¼% Dakin's solution is the solution currently used in practice as a standard of care.

The V.A.C. VeraFlo™ Dressing System is intended for use with V.A.C. VeraFlo™ Therapy as provided by the V.A.C. Ulta™ Therapy Unit. The V.A.C. VeraFlo™ Dressing was cleared under the V.A.C Ulta™ Negative Pressure Wound Therapy System 510(k) (K100657). Please see attached brochure for detailed information.

DATA COLLECTION FLOW SHEET

ASSESSMENTS	PRE-ED	TRAUMA	Clinic Visit	OR	IR	IN-PATIENT DAILY ASSESSMENT	DISCHARGE INFO		
Eligibility Criteria	X	X		X					
Demographics	X	X		X					
EMS Arrival Information	X	X							
Glasgow Coma Scale	X	X				X			
Informed Consent	X	X		X	X				
Vital Signs	X	X	X	X	X	X			
Mortality	X	X	X	X	X		X		
Life Saving Interventions	X	X		X	X	X			
Injury Information	X	X							
Blood Products	X	X		X	X	X			
Non-blood Fluids Medications Surgical Procedures	X	X	X	X	X	X			
Interventional Radiology				X	X				
Procedures		X	X	X	X				
First Available Labs		X		X					
Laboratory Results Highs and Lows/24hr Until Discharge		X		X	X	X			
Anesthesia Medications & Fluids	X	X		X	X				
Adverse Events/Serious Adverse Events	X	X	X	X	X	X	X		
Charlson Index							X		
Complications	X	X	X	X	X	X	X		
Injury Severity Score (ISS) Subject Disposition							X		
Past Medical History	X	X	X						
Trauma Registry Data							X		
End of Study Withdrew							X		



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