STUDY PROTOCOL

Evaluation of a Closed Incision Negative Pressure Dressing (PREVENA) To Prevent Lower Extremity Amputation Wound Complications

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This protocol has been written in accordance with current applicable guidelines (IDE for USA) as well as all other relevant additional references, medical and legal. The information herein is confidential and to be used in confidence for the conduct of the clinical trial according to written agreement.

PROTOCOL REVISION HISTORY

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1. SPONSOR RESPONSIBILITIES AND ADDRESSES

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2. ABBREVIATIONS AND DEFINITIONS

ADE	Adverse Device Effect
AE	Adverse Event
AKA	Above-Knee Amputation
BKA	Below-Knee Amputation
EC	Ethics Committee
CRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
HbA1C	Hemoglobin A1c
iNPWT	Incisional Negative Pressure Wound Therapy
IDE	Investigational Device Exemption
IRB	Institutional Review Board
LOS	Length of Stay
NPWT	Negative Pressure Wound Therapy
ROR	Reoperation Rate or Return to Operating Room
SAE	Serious Adverse Event
SC	Steering Committee
SOP	Standard Operation Procedures

3. PROTOCOL SUMMARY

Objectives	To evaluate the impact of a closed incision negative pressure dressing (PREVENA) on incidence of post-operative wound complications, and medical costs in patients undergoing lower extremity amputation who are enrolled in a clinical trial.
Study Design	This study is a prospective, multi-center, two-arm, unblinded, and randomized controlled trial. We will enroll up to 440 adults presenting for above-, or below-knee amputation across approximately five study sites. Consenting patients will be randomized to receive either the PREVENA dressing, or usual care dressing on their amputation incision for five or six days post-procedure. Patients will return for a follow-up assessment at 30 days.
Number of Subjects	Up to 440 subjects will be enrolled in this study
Selection Criteria	**Inclusion criteria** 1. Male or female adults 18 years or older 2. Patients undergoing above-knee amputation (includes the revision of emergency guillotine amputations) 3. Patients undergoing below-knee amputation (includes the revision of emergency guillotine amputations) 4. Informed Consent signed by patient **Exclusion criteria** 1. Minors under 18 years 2. Women who are pregnant or breastfeeding 3. Patients undergoing emergent or guillotine amputation 4. Patients having BOTH legs amputated 5. Patients with sensitivity to silver 6. Unwilling or unable to provide informed consent 7. Inability to comply with planned study procedures
Primary Endpoint	▪ Incidence of any post-operative wound complications at 30 days including: dehiscence (skin or fascia), seroma, lymph leak, infection (deep or superficial), hematoma, ischemia and necrosis
Secondary Endpoints	▪ Index length of stay ▪ 30 day return to operating room for wound complications ▪ 30 day hospital readmissions for wound complications
Exploratory Endpoints	▪ 30 day hospitalization costs ▪ 30 day variable hospital costs
Scheduled follow up	For evaluation of the primary and secondary endpoints, subjects will be followed for a period of 1 month (30 days). Data will be collected at the following time-points: ▪ Baseline for demographics, vital signs, and medical history ▪ Day of surgery ▪ At discharge for dressing and wound assessment data ▪ 30 days (±5 days) after discharge for wound assessment data and clinical outcomes For evaluation of the exploratory endpoints, data on hospitalization and variable costs will be collected after final accounting is completed and UB04 billing data becomes available.

4. INTRODUCTION

Perioperative wound complications, are common following lower extremity amputation, with occurrence rates of 10% to 34% among amputees [1, 2]. At Thomas Jefferson University/Hospital (TJU/H), approximately 15% of patients experienced some form of wound complication following lower extremity amputation. Lower extremity amputation complications in vascular surgery can be devastating in terms of patient morbidity and mortality, and are costly for the institution in terms of extended length of stay or readmission.

The PREVENA™ PEEL & PLACE™ Dressing Kit ("Prevena"; KCI USA, Inc., San Antonio, TX) is marketed in the U.S. as a dressing that is used with a negative pressure pump. Prevena is intended to manage the environment of clean, closed surgical incisions (i.e., sutured or stapled) that continue to drain via the application of negative pressure wound therapy (NPWT), maintaining a closed environment and removing exudate. NPWT was initially developed to assist patients with open chronic and acute wounds that were difficult to heal and then found to be useful over closed incisions. Several recent studies in cardiac and orthopedic surgery demonstrated significant reductions in wound complications in high-risk populations by applying a negative-pressure dressing over the primarily closed incision [3-5]. In addition, a recent meta-analysis of 10 studies (1089 patients, 1311 incisions) assessing negative pressure wound therapy suggested this as an effective strategy for reducing seroma formation and infections [6].

In a recently completed randomized controlled trial by the Principal Investigator (PI), Dr. DiMuzio, Prevena reduced rate of infection by as much as 50% in sternal and groin incisions (manuscript in review [7]). This finding informed the development of this project. The Prevena dressing is applied immediately post-surgery (i.e., in a sterile field) to clean, closed incisions for a minimum of 2 days and up to a maximum of 7 days. Prevena is a disposable, single-patient use dressing designed to protect incisions from external contaminants, and remove fluid and infectious materials by delivering continuous negative pressure. The proposed randomized controlled trial will assess the impact of the Prevena dressing plus NPWT versus usual care on wound complication rates for lower extremity amputations.

5. STUDY OBJECTIVES

5.1. Primary Objective

The primary outcome of this study is reported wound complications, specifically:

- Dehiscence (skin or fascia)
- Seroma
- Lymph leak
- Infection (superficial or deep; see CDC Surgical Site Infection criteria on pg. 9.8 to 9.10 [8])
- Hematoma
- Ischemia
- Necrosis

Complications will further be classified as major wound complication if they require intravenous or oral antibiotics, reoperation and/or hospital readmission.

5.2. Secondary Objectives

We will assess the impact of the Prevena dressing on the following secondary outcomes:

1. Length of stay (LOS): index LOS is defined as days from operation to discharge; 30d LOS is defined as the index LOS plus all readmission days within 30d related to any wound complication

2. 30-day Return to Operating Room (ROR): Reoperation for wound complication within 30 days involving incision and drainage in the operating room; opening the skin to drain a superficial soft tissue infection at bedside or in the office is not considered reoperation

3. 30-day hospital readmissions: Rehospitalization for wound complication within 30 days

5.3. Exploratory Objectives

Finally, the following exploratory outcomes will be assessed:

1. 30-day hospitalization costs: Index hospitalization costs as well as all readmission days within 30d related to any wound complication

2. 30-day hospital variable costs: Variable costs (not charges) for each admission obtained from hospital administration.

6. STUDY DESIGN

The PREVENA-AMP study is a prospective, multi-center, two-arm, unblinded, and randomized controlled trial of patients undergoing lower extremity amputation (above- or below-the-knee). Patients will be randomized to receive either the Prevena dressing or usual care for five or six days after the procedure on a lower extremity amputation incision. Patients will complete a follow-up assessment at approximately 30 days post-discharge. Demographic and clinical information will be collected through medical record review at enrollment, post-procedure, and at approximately 30 days post-discharge by participating sites.

6.1. Enrollment

Patients presenting to Vascular and Endovascular Surgery for above-knee amputation (AKA) or below-knee amputation (BKA) will be screened for study eligibility. If a subject is willing to participate in the study, a written informed consent for the study must be obtained prior to any study related procedure and all eligibility criteria must be confirmed.

6.2. Selection of Subjects

6.2.1. Informed Consent

The consent form is written in accordance with applicable data privacy acts and FDA Regulations and approved by the responsible Institutional Review Board (IRB).

The informed consent process will take place prior to the planned procedure. The investigator or responsible staff will explain the nature, purpose and risks associated with the study. The patient will be given sufficient time to consider the study's

implications before deciding whether to participate. Patient information materials created by the Investigators and Coordinating Center must be approved by the IRB before use.

A signed, IRB/EC-approved consent form must be obtained from the patient prior to the performance of any protocol-related testing or procedures unless obtained as part of standard care. The consent process must be performed by a designated clinical study team member authorized by the IRB to consent patients and listed on the Delegation of Authority Log as having privileges to consent patients. A signed/dated copy of the consent form must be maintained in the study files and a copy provided to the patient.

6.2.2. Number of Subjects

Up to 440 subjects will be included in this study, 220 in each of the two arms.

6.2.3. Subject Inclusion Criteria

1. Male or female adults 18 years or older
2. Patients undergoing above-knee amputation (includes the revision of emergency guillotine amputations)
3. Patients undergoing below-knee amputation (includes the revision of emergency guillotine amputations)
4. Informed Consent signed by patient

6.2.4. Subject Exclusion Criteria

1. Minors under 18 years
2. Women who are pregnant or breastfeeding
3. Patients undergoing emergent or guillotine amputation
4. Patients having BOTH legs amputated
5. Patients with sensitivity or allergy to silver or adhesive.
6. Unwilling or unable to provide informed consent
7. Inability to comply with planned study procedures

7. STUDY DEVICE

7.1. PREVENA™ PEEL & PLACE™ Dressing Kit

This study will assess the impact of a market-released surgical dressing that has been FDA-cleared in the US (K100821) on wound complications. The PREVENA™ PEEL & PLACE™ Dressing Kit ("Prevena"; KCI USA, Inc., San Antonio, TX) protects the incision from external contamination, helps hold incision edges together, removes fluid and infection materials, and delivers continuous negative pressure at up to -125mmHg for a maximum of seven days in combination with a negative pressure pump. The dressing is easy to apply and use in the operating room by the surgeon. **Detailed information is found in the Prevena Clinician's Guide.**

PREVENA™ PEEL & PLACE™ Dressing Kit components include:

1. The PREVENA™ PEEL & PLACE™ Dressing that is applied over clean, sutured or stapled incisions in a simple peel-and-place process, with multiple dressing options for linear incisions between 5 to 17 inches long.
   - The dressing has a built-in pressure indicator that when compressed indicates that the negative pressure in the system is between -75mmHg to -125mmHg. A raised pressure indicator button indicates that the negative pressure is less than 75mmHg.
   - A polyurethane coated, polyester fabric interface layer with 0.019% ionic silver wicks fluid from the skin surface. The silver is not intended to treat infection but only to reduce bacterial colonization within the fabric.
   - The polyurethane foam bolster that covers the interface layer has a pore size of 400-600 microns and a violet colorant; the foam magnifies negative pressure to the incision site.
   - A polyurethane film with acrylic adhesive provides adhesion of the dressing to the skin surrounding the incision.
   - A polyurethane shell encapsulates the foam bolster and interface layer, providing a closed system that allows patients to shower with dressing in place.
   - A connecting tube that is integrated with the dressing for connection to a negative pressure pump.
2. PREVENA™ Therapy V.A.C. ® Connector, which is required for connection of PREVENA™ Incision Dressings to approved V.A.C. ® Therapy Units.
3. PREVENA™ Patch Strips, which may be used to help seal leaks around the dressing.
4. All patient-contact materials are free of latex and DEHP [Di(2-ethylhexl)phthalate].

7.2. Packaging

The PREVENA-AMP study device is FDA 510(k) cleared and will be used with the standard packaging.

7.3. Instruction for Use

The device will be used as specified in the relevant Instructions for Use.

7.4. Required Training on Study Device

Negative pressure dressings are now commonplace throughout the hospital and operating room. As such, formal education regarding the proper application of the Prevena dressing is considered an ongoing process during the practitioner's surgical education.

8. NEGATIVE PRESSURE WOUND THERAPY

8.1. Negative Pressure Wound Therapy using PREVENA™ PEEL & PLACE™ Dressing Kit

In combination with a negative pressure pump (V.A.C. ® Therapy Unit, KCI USA, Inc.), the Prevena dressing is designed to provide negative pressure wound therapy (NPWT) over surgical incisions (incisional NPWT). Negative pressure wound therapy is the controlled application of subatmospheric pressure to a wound using an electrical pump to intermittently or continuously convey subatmospheric pressure through connecting tubing to a specialized wound dressing. Application of negative pressure to an incision site that is closed via staples or sutures helps draw

the incision edges together and removes fluid from the incision site. The occlusive drape of the dressing provides a negative pressure environment and protects the incision from external contamination. The Prevena dressing contains 0.019% ionic silver that may help reduce bacterial colonization within the fabric.

For initiation of therapy, the Prevena dressing can be connected to a KCI V.A.C. ® Therapy Unit to deliver continuous negative pressure at -125 mmHg through the dressing to the incision site. The following Therapy Units are compatible with the Prevena dressing and can be used by study sites to provide negative pressure (**Detailed information is found in the Clinician's Guide for each respective Therapy Unit**):

- INFOV.A.C. ™
- V.A.C.RX4™
- V.A.C. SIMPLICITY™
- ACTIV.A.C. ™
- V.A.C. FREEDOM™
- V.A.C.ULTA™

Dressing application, negative pressure application, and dressing removal will only be conducted by a physician or designee. Patients using Prevena should contact the physician or nurse if the therapy unit turns off before therapy ends or if any of the following findings occur:

- Bleeding develops suddenly or in large amounts during therapy
- There are signs of allergic reaction or infection
- The canister is full of fluid
- System alerts need to be addressed

9. STUDY INTERVENTION

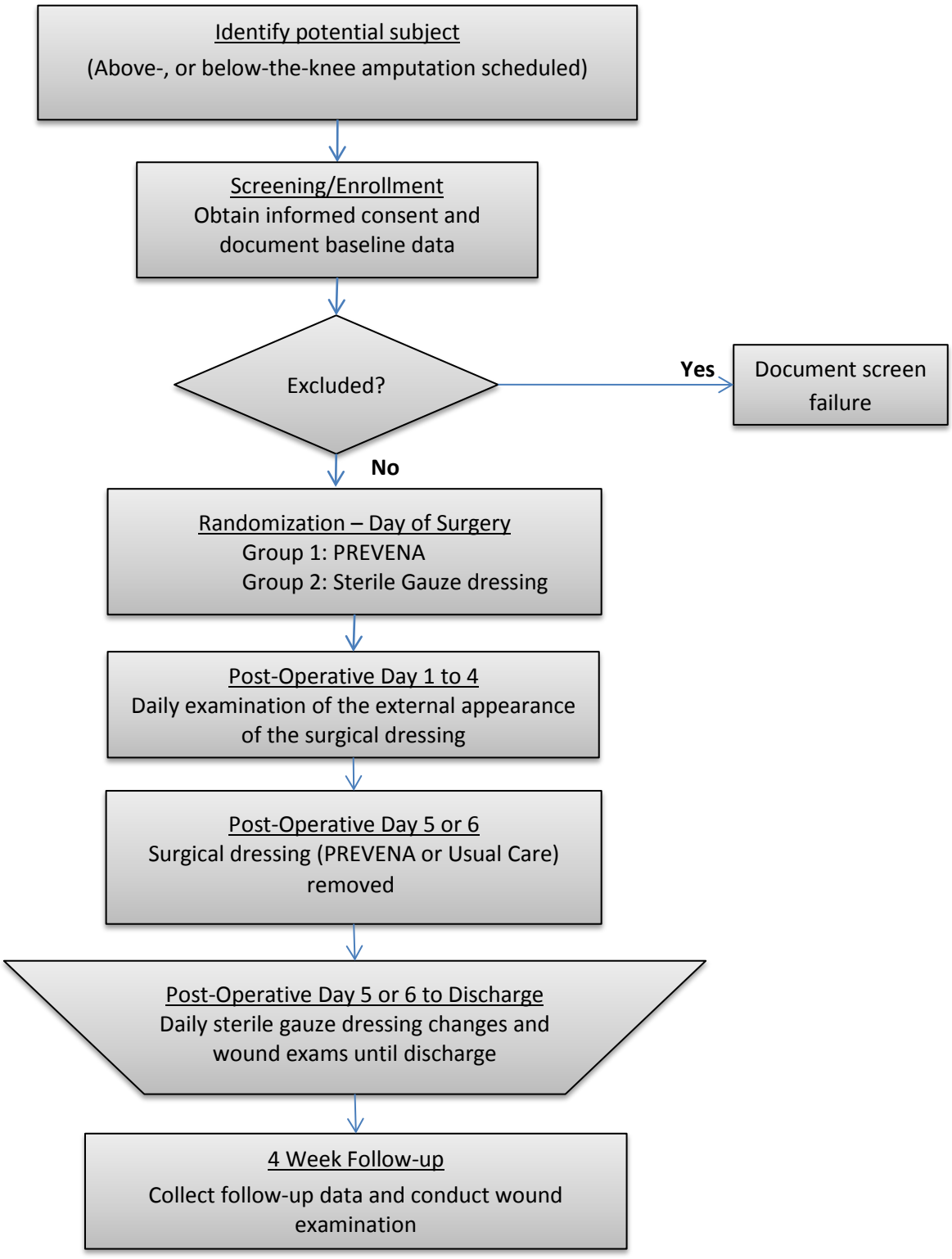
9.1. Treatment Groups

Enrolled subjects will be randomized to one of two groups prior to their surgical procedure:

- Group 1: PREVENA
- Group 2: Usual Care

Subjects randomized to the PREVENA group will have the Prevena dressing applied to their surgical incision while in the operating room and will receive NPWT using an V.A.C. ® Therapy Unit that is compatible with the dressing. Subjects randomized to the Usual Care group will have a sterile gauze dressing supplemented with an Ace wrap applied to their incision while in the operating room. For both treatment groups, the surgical team will examine the surgical dressing daily until post-operative day (POD) 5 or 6. On POD 5 or 6, all surgical dressing will be removed and replaced with sterile gauze covered by an Ace bandage. After the initial surgical dressing is removed, the care team will examine the incision daily until the patient is discharged from the hospital. Dressing and wound examination notes documented in the subject medical record will be abstracted by study personnel for inclusion in the Case Report Form (CRF).

10. Study Flow



11. STUDY SCHEDULE

11.1. Detailed Visit Schedule

The following visit schedule applies to subjects who met all eligibility criteria, and are enrolled in the PREVENA-AMP study.

11.1.1. Screening/Enrollment
Determination of eligibility and enrollment
Collect demographics and baseline data from medical record

11.1.2. Randomization
Randomized to either PREVENA Group or Usual Care (Sterile Gauze Dressing) Group

11.1.3. Day of Surgery
Given either Prevena dressing or Usual Care (Sterile Gauze Dressing)

11.1.4. Post-Operative Days 1 – 4
Daily examination of the external appearance of the surgical dressing and assessments of the dressing documented in medical record

11.1.5. Post-Operative Day 5 or Day 6
Surgical dressings (PREVENA and Usual Care) removed, and replaced with sterile gauze dressing supplemented with an Ace wrap

11.1.6. Post-Operative Day 5 or 6 to Discharge
Wound examined and dressing changed daily until discharge; wound assessments documented in medical record
Collect POD 1 to Discharge dressing/wound assessment data from medical record

11.1.7. Post-Discharge Follow-up at Day 30
On day 30 (±5 days), incision examined and wound assessment documented in medical record
Collect follow-up wound assessment data from medical record
Collect follow up data on readmissions, ROR, LOS, and wound complications from medical record
Collect data on costs from hospital administration records

11.2. Overview of visits

	Screening/ Enrollment	Prior to Surgery	Surgery	POD 1 to 3	POD 5 (±1 day)	POD 5 or 6 to Discharge	Discharge to 30 Days (±5 days) "1 month"
Enrollment	X						
Baseline data collection	X						
Physical Examination	X						
Randomization		X					
Dressing application (PREVENA or Usual Care)			X				
Daily dressing examinations				X			
PREVENA and Usual Care surgical dressings removed on post-operative day 5 or day 6					X		
Daily wound examinations and dressing changes until discharge						X	
Follow-up visit with surgical team to examine wound							X

11.3. Duration of the study

An individual subject's participation is expected to be 30 days. With an expected enrollment period of up to 15 months for 440 subjects, and a follow-up period of 1 month, the overall study duration is calculated to be approximately 22-30 months.

12. VISIT PROCEDURES

12.1. Screening/Enrollment

Patients presenting for above-knee amputation (AKA) or below-knee amputation (BKA) will be screened for inclusion in the study. If they are not eligible for study participation, study personnel will document the reason for screen failure, and patients who do not meet the eligibility criteria will not be approached about the PREVENA-AMP study. Patients who meet eligibility criteria will be approached and asked about study participation. If a patient is unsure about participating in the study, they will be informed that they have the right to refuse participation and that the study is voluntary. They will be told that they will still receive standard of care regardless of their decision to participate. If a patient is not interested in the study, study personnel will accommodate the patient's preference and no additional recruitment attempts will be made.

If the patient continues to be eligible for participation in the study and expresses interest in participating, the study team will:

1. Document eligibility criteria data
2. Obtain informed consent and enroll the patient in the PREVENA-AMP study
3. Document informed consent process

12.2. Baseline Data Collection

Upon enrollment, the following data will be collected for each subject:

- age, gender, race, ethnicity
- indication for amputation (tissue loss, rest pain)
- classification of tissue loss (ulceration, gangrene, presence of infection)
- prior vascular procedures (specifically prior prosthetic bypass which will be transected)
- medical co-morbidities (diabetes mellitus/HbA1C, dialysis dependence, active smoker, chronic venous insufficiency, end-stage renal disease, congestive heart failure)
- BMI, blood pressure, pulse examination, and ankle-brachial index (if available)

12.3. Randomization

Prior to the surgical procedure, subjects will be randomized on a 1:1 basis to either the PREVENA arm or the Usual Care arm.

Randomization will be stratified by site and conducted in permuted blocks. The stratification insulates the randomization of one site from another which allows for subgroup analyses by site, while permuted blocks ensures balanced allocation between treatment arms.

Each site will receive a randomization scheme that contains a series of randomized group assignments and randomization IDs. As subjects are enrolled in the study, their subject ID will be assigned to a corresponding randomization ID. This information will be recorded in the CRF.

12.4. Day of Surgery

All subjects will undergo their amputation procedure as scheduled. While in the operating room, after flap closure, subjects will receive the dressing that corresponds to their group assignment:

- **Group 1 (PREVENA Arm):** Subjects randomized to the PREVENA arm will receive the Prevena negative pressure dressing on their incision
- **Group 2 (Usual Care):** Subjects randomized to usual care will receive sterile gauze and Ace wrap compression dressing on their incision

The use of an external splint will be determined by the attending surgeon.

12.5. Dressing Monitoring (Post-Operative Days 1 to 4)

The external appearance of the surgical dressing for both PREVENA and Usual Care groups will be examined by the surgical team on daily inpatient rounds.

12.6. Wound Monitoring (Post-Operative Day 5 or Day 6 to Discharge)

On post-operative day 5 or day 6, the surgical dressings (both PREVENA and usual care) will be removed and replaced with a new sterile gauze dressing supplemented by an Ace wrap. The sterile gauze dressing will be changed daily, and the incision will be assessed for wound complications during the dressing change every day until discharge from the acute care setting.

12.7. Discharge

Following discharge, the patient and/or caregivers will provide standard wound care that involves keeping the incision clean, dry and covered with a gauze dressing supplemented by an Ace wrap.

12.8. Follow-Up Visit (Discharge to Day 30 ± 5 days)

The final study visit will take place approximately 30 days after discharge. During this follow-up visit, the wound will be assessed for wound complications. For incisions closed with staples, these would be removed between post-operative days 30-42 at the discretion of the surgeon.

13. SAFETY

The investigator is responsible for monitoring the safety of subjects enrolled into the study at the study site. The investigator or qualified designee will enter the required initial and follow-up information regarding events on the appropriate CRF. Investigators are responsible for following all serious adverse events (SAEs) until resolution, stabilization, or the event is otherwise explained, and to report serious adverse events as well as serious injury or death that were related to (caused by or contributed to) the Prevena dressing in accordance with their local IRB/EC requirements. Investigators should follow usual clinical practice at their institutions for reporting serious events to the regulatory authorities.

13.1. Labeled Adverse Device Effects

Expected adverse device events are determined to be mild and are related to the interface (polyurethane drape) between the device (Prevena dressing) and the subject. In this study, any skin irritation that is transient (i.e., resolves within 24 hours following device use and requires no medical intervention), will not be classified as an adverse device effect.

<u>Dressing</u>

- Mild skin irritation of the skin under the enclosed dressing
- Discomfort with having to wear an occlusive dressing that may be twice the size of normal dressing

<u>V.A.C. ® Therapy Unit</u>

- Inadequate seal of the Prevena dressing over the patient's skin due to improper placement or the patient shifting position could prevent adequate negative pressure delivery upon the wound
- The inconvenience of having to keep the negative pressure pump attached to the incision site

14. STATISTICAL ANALYSIS

14.1. Study Hypothesis

The primary hypothesis for this study asserts that the application of a negative pressure wound therapy dressing (Prevena) and negative pressure pump over a closed lower extremity amputation

incision will decrease the wound complication rate at 30 days in patients undergoing lower extremity amputation, as compared to patients receiving standard care. The secondary hypothesis suggests that patients who receive Prevena will have reduced LOS, ROR, and readmission rates compared with patients who receive usual care.

14.2. Analysis Plan

We will carry out initial descriptive analysis to identify outliers, such as measurement and recording errors, logical inconsistencies in data, and values extreme in the marginal distributions of all study variables. Data summaries will be produced both for the combined sample, and separately by treatment arm. Continuous variables will be presented as means and standard deviations or, if substantially skewed, presented as medians and first and third quartiles and then transformed using a Box-Cox power transformation for parametric analysis. Categorical variables will be presented as frequencies and percentages. The baseline characteristics will be compared between the treatment arms to identify potential confounding variables. Men and women will be examined separately first to assess whether the treatment effect might depend on sex. Similarly, the associations and interaction effects of other variables (e.g., age and race) will be explored. Participant flow will be described using a CONSORT style diagram.

14.3. Primary Endpoint Analysis

The primary endpoint will be the difference in mean wound complication rates after 1 month. A Yates Chi-Square test (2x2 contingency table) will be used to determine if the differences between the wound complication rates of the two randomized treatment groups (PREVENA versus Usual Care) are statistically significant at the 0.05 level.

14.4. Secondary and Exploratory Endpoint Analysis

Descriptive analyses of the secondary and exploratory endpoints will be conducted using the previously described methods for continuous and categorical endpoints in order to characterize both the combined sample, and to compare by treatment group. Student's t-test will be used to evaluate if the difference in the secondary endpoints (index and 30-day LOS; total number of hospitalizations at 30 days) and exploratory endpoints (hospitalization costs; hospital variable costs) between the two groups is statistically significant at the 0.05 level. In addition, Yates Chi-Square test will be used to compare the proportion of patients in each group with reported ROR, or readmission within 30 days ($P<.05$ considered significant). Finally, respective multivariable logistic regression models will characterize the odds of 30 day ROR and odds of 30 day readmission, using study variables found to be related to return and readmission in descriptive analysis.

14.5. Justification of the Sample Size

Based on a review of the literature, perioperative wound complications occur among 10% to 34% of lower extremity amputees. We postulate a wound complication rate of 22% for this study.

Previous studies have shown that, among femoral incision patients, Prevena reduced the relative risk of major wound complications by 60.8% (from 21.7% among controls to 8.5% using Prevena). Assuming a similar, but somewhat attenuated, risk reduction of 50% among amputees, we would expect the major wound complications among patients treated with Prevena to be 11.0% in this study. Assuming major wound complication rates are 22% and 11% in the control and Prevena populations, and using an O'Brien-Fleming early stopping boundary[9] for an interim look at the data, suggests that in order to maintain an overall 5% type I error rate, the study would need data on up to n = 210 patients per group to have 80% power for detecting this (or a greater) difference in complication rates by two-sided Z-tests. The operating characteristics of this group sequential testing approach are provided in the table below. We expect 5% attrition from mortality and/or loss to follow-up, so our overall recruitment goal will be n = 220 per group (N = 440 overall).

Interim analysis operating characteristics using O'Brien-Fleming stopping bounds.

Look	Expected Complications	Expected Sample Size	Z-test Lower Bound	Z-test Upper Bound	Alpha	Power
Interim	52 (75%)	315 (75%)	-2.34	2.34	0.019	0.55
Final	70 (100%)	420 (100%)	-2.01	2.01	0.044	0.80

14.6. Interim Analysis

Interim analysis for early stopping of the trial for efficacy will be conducted once prior to enrolling the planned complete sample size. This analysis will be conducted at 75% of the expected number of patients having the primary endpoint (i.e., 52 patients with major wound complications).

15. DATA HANDLING AND RECORDKEEPING

15.1. Data Collection

The investigator, sub-investigator(s), or study coordinator participating in the study will document all data required by the protocol.

Each participating site will provide data on LOS, variable costs, and hospitalization costs for each subject to facilitate analysis of the secondary endpoints.

In addition, any contact with the subject via telephone or other means that provide significant clinical information must be documented.

Any changes to information in the source documents must be initialed and dated on the date the change is made by a clinician authorized to make the change.

15.2. Study Documentation

Throughout the conduct of the study, all required data will be entered into the CRF for each subject. The investigator should ensure the accuracy, completeness, and timeliness of the data reported to the in the CRFs and in all required reports. Data entered into the CRF must be consistent with source documents. Any change or correction to CRF will be captured. The clinical site will provide study data by recording data in CRF. In cases of subject-reported data, the CRF will be the source record.

15.3. Query Generation and Resolution

Queries will be generated based upon anomalous or missing data and will be tracked. Once all queries are resolved, the database will be verified by ensuring all study files were loaded completely and correctly.

15.4. Data Storage

Access to data maintained in the EDC System is strictly limited to authorized personnel.

15.5. Inspection of Records

Periodically the Coordinating Center may review the Investigator study file and the study data to verify compliance with applicable regulations and the protocol, and to verify accuracy of the data.

15.6. Study Files and Record Retention

The investigator must maintain adequate and accurate records as specified in Essential Documents for the Conduct of a Clinical Trial (E6, Section 8 of the ICH Guideline for GCP) to enable the conduct of the study to be fully documented and the study data to subsequently be verified.

Essential documents must be retained until at least 2 years after notification that the investigations have been discontinued **OR** 2 years after the last approval of a marketing application. The investigator must notify the Coordinating Center prior to destroying any clinical study records.

15.7. Regulatory Documentation

Documents that must be provided to the Coordinating Center prior to study initiation are:

- Signed, dated current (within 2 years) curriculum vitae of Investigator and Sub-Investigator(s)
- Current professional license for Investigators and study personnel
- Financial disclosure for Investigators and study personnel
- Proof of current human subjects training for Investigators and study personnel
- Signed (original), dated Protocol
- Signed (original), dated IRB Authorization Agreement (including the institution's Federal-Wide Assurance (FWA) number if available) naming Jefferson as the IRB of record
  OR

- Assurance that the IRB/EC complies with requirements set forth in Title 21 Part 56 of the Code of Federal Regulations (required documentation consists of name and address of the IRB/EC, a current list of members including title, gender, occupation and any institutional affiliation of each member or the FWA number from the Department of Health and Human Services may be substituted for this list)
- Written notification (copy) to the Investigator from the IRB/EC approving the protocol
- IRB/EC approved informed consent (copy) and any other adjunctive materials to be used in the study as required

16. ETHICAL CONSIDERATIONS

16.1. Institutional Review Board (IRB)

The investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (if used), and any other written information to be provided to subjects. The investigator should also provide the IRB with a copy of the product labeling information and any updates. The investigator will provide the IRB with reports, updates, and other information (e.g., safety updates and protocol amendments) as required by regulations.

16.2. Protocol Deviations

An investigator is required to conduct this study in accordance with the signed Investigator's Agreement, this Investigational Plan, applicable laws and FDA regulations, and any conditions of approval imposed by the reviewing IRB and FDA. According to FDA regulation 21 CFR § 812.150(a)(4), an investigator shall notify the sponsor (Thomas Jefferson University) 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 no later than five working days after the emergency occurred. Except in such an emergency, prior approval by the Coordinating Center is required for a change in or deviations from a plan and, if these changes or deviations could affect the scientific soundness of the plan or the rights, safety or welfare of human subjects, FDA and IRB/EC approval may also be required in accordance with 21 CFR § 812.35(a).

A list of subjects with protocol deviations will be compiled based on entry criteria deviations as well as deviations from study conduct and assessments. Prior to data base lock, an evaluation of subjects with significant protocol deviations will be performed to assess the appropriateness of their inclusion in the analysis.

16.3. Risk Analysis and Confidentiality

16.3.1. Risk Determination of the Study

The Prevena dressing has been cleared by FDA to provide negative pressure wound therapy to surgical incisions. The dressing is intended for hospital use, with placement occurring within the

operating room. The purpose of this study is to evaluate the effect of the Prevena dressing on wound complication rates for adult patients undergoing lower extremity amputation.

This study is considered to be of minimal risk to the patients receiving Prevena. NPWT is widely accepted and effective for treating deep wounds, and the risks associated with its use in this study are reasonable in terms of knowledge gained and potential benefits to patients. By its nature, use of NPWT on surgical incisions may be associated with minor side effects. Prevena may cause minor discomfort, especially in a patient who has not previously used NPWT. In this study, these side effects will not be classified as adverse events unless they do not resolve within a reasonable period of time when NPWT is discontinued.

Subjects should be encouraged to discuss any issues they are having with NPWT during the study. The investigator should assess for changes in the health or well-being of the subject in response to general, non-directed questioning. Side effects should be documented on the site's source documents. Any transient side effects, at a minimum, should be documented in the clinic record.

16.3.2. Subject Data Confidentiality

All information and data collected for the PREVENA-AMP study concerning subjects or their participation in this investigation will be considered confidential. Only authorized site personnel or Coordinating Center personnel will have access to these confidential files. All data will be handled in accordance with applicable local laws. Authorized FDA personnel or Regulatory Authorities have the right to inspect and copy all records pertinent to this investigation. All data used in the analysis and reporting of this investigation will be without identifiable reference to specific subject name.

17. QUALITY CONTROL AND QUALITY ASSURANCE

Quality Control is defined as the operational techniques and activities, such as monitoring, undertaken within the quality assurance system to verify that the requirements for quality of the study related activities have been fulfilled. Quality Control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

17.1. Site Selection

The sites must have adequate experience, time, staff, and facilities to perform all required duties. Sites must agree to permit clinical trial related monitoring, audits, IRB review, and regulatory inspections, providing access to source data/documents, as appropriate.

17.2. Site Training

The Coordinating Center will conduct a site initiation conference call with each site to review relevant documentation such as the clinical protocol, Prevena device usage instructions, and investigator's obligations with site study personnel. In addition, training on the Case Report Form (data collection) will be conducted. If new study staff members are employed by the site after the initiation meeting, experienced site personnel must train new employees as noted above and document the training using the Training log provided by the Coordinating Center.

17.3. Audits and Inspections

The Sponsor (or designee), FDA, NIH and any other regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with Federal regulations. The investigator must immediately notify the Coordinating Center of an upcoming FDA or other regulatory agency inspection. Audits may also be conducted by representatives of the Coordinating Center.

18. RESPONSIBILITIES

18.1. Clinical Investigator Responsibilities

With the approval of their institution's IRB/EC, qualified investigators will conduct the PREVENA-AMP study in accordance with the Declaration of Helsinki: "Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects". Each site principal investigator and their sub-investigators are responsible for the following:

- Completion of all required agreements
- Screening and evaluation of subjects
- Strict adherence to the Clinical Protocol, Manual of Procedures and all Federal Regulations
- Supervising device use
- Obtaining informed consent prior to study related procedures and the collection of data during study and follow-up examinations in a timely manner
- Timely reporting of all SAEs and UADEs
- Providing death notes, when applicable

It is acceptable for the site principal investigator to delegate one or more of the above functions to an associate or sub-investigator, however, the site principal investigator remains responsible for proper conduct of the clinical investigation and signing an investigator agreement. The investigation is non-transferable to other centers attended by the investigator unless prior approval is obtained from the appropriate IRB/EC and the Coordinating Center.

18.2. Sponsor Responsibilities

The Sponsor (Thomas Jefferson University) will provide each site with study materials. The Coordinating Center (Jefferson Clinical Research Institute) will train study personnel on the clinical study protocol and procedures. Randomization procedures for all enrolling sites will be managed centrally through the Coordinating Center and the permuted block sizes will be kept confidential from study personnel conducting enrollment. Coordinating Center representatives will ensure that the study is progressing as expected, study data are accurate and up to date, data recording is complete, and protocol deviations are recorded and reviewed with the PI. Throughout the study period, the Coordinating Center representative will be available to address any issues that may arise. This availability includes access by phone and/or e-mail.

19. STUDY ORGANIZATION AND COMMUNICATION

19.1. Steering Committee, Study Team and Communications

The Steering Committee (SC) includes the lead investigators from each site. Any required modifications to the protocol will be reviewed and approved by the SC prior to implementation.

The Study Team, PI, Sub-I, or designee(s) will meet monthly via telephone/video conference call, or in-person.

20. REFERENCES

1. Hasanadka, R., et al., *Predictors of wound complications following major amputation for critical limb ischemia.* J Vasc Surg, 2011. **54**(5): p. 1374-82.
2. Belmont, P.J., Jr., et al., *Risk factors for 30-day postoperative complications and mortality after below-knee amputation: a study of 2,911 patients from the national surgical quality improvement program.* J Am Coll Surg, 2011. **213**(3): p. 370-8.
3. Stannard, J.P., et al., *Incisional negative pressure wound therapy after high-risk lower extremity fractures.* J Orthop Trauma, 2012. **26**(1): p. 37-42.
4. Pachowsky, M., et al., *Negative pressure wound therapy to prevent seromas and treat surgical incisions after total hip arthroplasty.* International Orthopaedics, 2012. **36**(4): p. 719-722.
5. Grauhan, O., et al., *Prevention of poststernotomy wound infections in obese patients by negative pressure wound therapy.* The Journal of Thoracic and Cardiovascular Surgery, 2013. **145**(5): p. 1387-1392.
6. Hyldig, N., et al., *Meta‐analysis of negative‐pressure wound therapy for closed surgical incisions.* BJS, 2016. **103**(5): p. 477-486.
7. Kwon, J., et al., *A Randomized Clinical Trial Evaluating Negative-Pressure Therapy to Decrease Vascular Groin Incision Complications*. 2018, Journal of Vascular Surgery.
8. National Healthcare Safety Network. *Surgical Site Infection (SSI) Event*. 2018 [cited 2018 June 25]; Available from: http://www.cdc.gov/nhsn/PDFs/pscManual/9pscSSIcurrent.pdf.
9. O'Brien, P.C. and T.R. Fleming, *A multiple testing procedure for clinical trials.* Biometrics, 1979. **35**(3): p. 549-56.

21. SIGNATURES

The trial will be conducted in accordance with the ICH E6 Good Clinical Practice, and applicable Federal and state Regulations or guidelines and the executed institutional agreements. Furthermore, the Investigator attests to the following:

- I confirm that I have read the above-mentioned protocol and its attachments.
- I agree to conduct the described trial in compliance with all requirements from the protocol.
- I agree that changes to the protocol will not take place without prior agreement from the Sponsor and documented approval from the designated Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants.
- I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator's Signature: _____ **Date:** _____

Investigator's Name: _____

Investigator's Institution: _____