Protocol for

PICO-LEB: Standard Versus PICO Dressings in Lower-Extremity Bypass Patients

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Statistical Analytic Plan (Section 8, pages 13-14)

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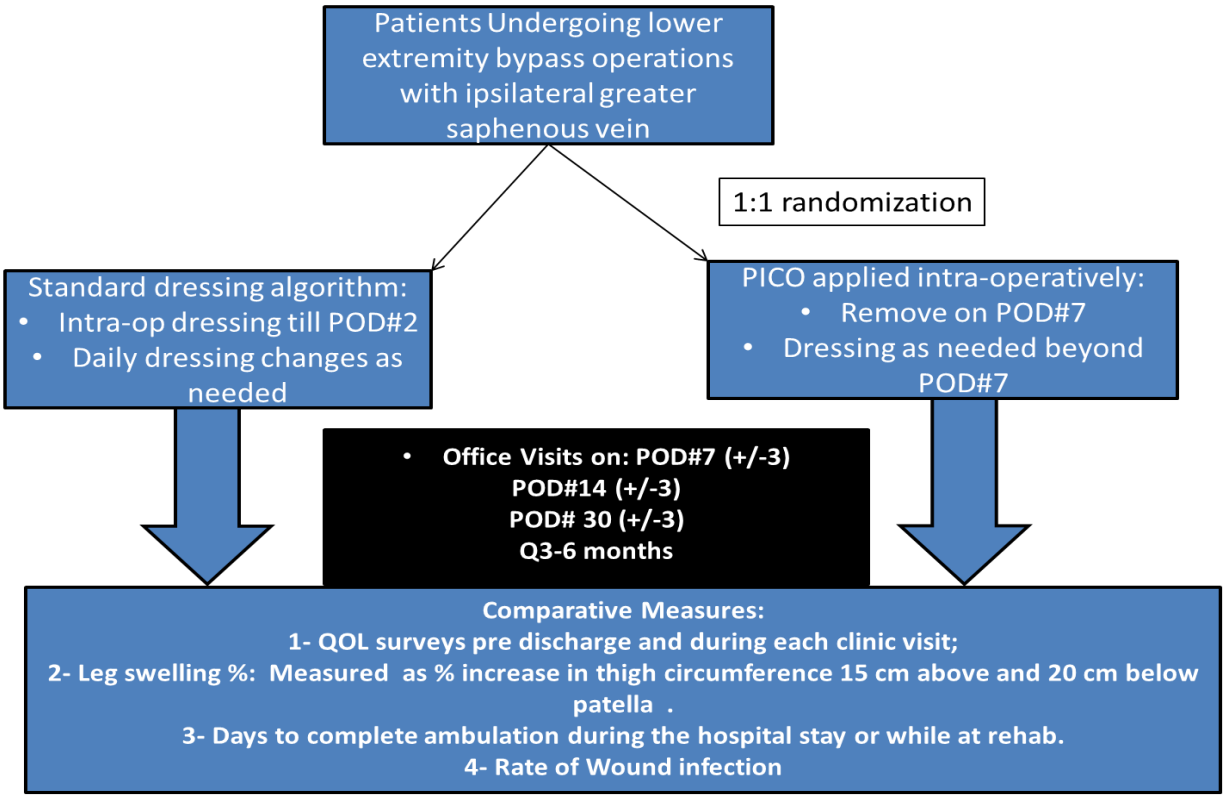
Trial Summary

The objective of this study is to compare the effectiveness of standard dressings and PICO single-use negative pressure dressings in post-operative lower extremity bypass patients. This study will compare the dressings' ability to decrease swelling, decrease post-operative infection, and improve mobility and quality of life measures.

Subjects will be asked to participate in this study because they will undergo a lower extremity bypass using the ipsilateral great saphenous vein. Subjects will then be randomized to two post-operative treatment groups. One group will receive standard sterile gauze and the other will receive PICO single-use negative pressure dressings. Both groups will be assessed for study measures in follow-up clinical visits up to 30 days.

Trial Overview



Schedule of Activities

			Post Procedure				
	Base-line	**Immed. Post-op**	**2 Days**	**7 (±3)**	**14 (±3)**	**30 (±3)**	**Q3-6 mo.**
Informed consent	X						
Medical history	X						
Physical examination and medications	X						
Focused peripheral vascular history	X						
In-person clinical evaluation (physical examination; update medical/vascular history and medications)	X			X	X	X	X
Assessment symptoms	X			X	X	X	X
Pain scale	X			X	X	X	X
Renal function	X			X	X	X	X
Vital Status	X			X	X	X	X
Quality of Life (VascuQoL, SF-12, EuroQoL EQ-5D)	X	X		X	X	X	X
Les swelling % measured	X	X	X	X	X	X	X
Remove moist dressing (standard wound care only)			X				
Remove PICO dressing				X			
Additional dressings as needed				X	X	X	X
Adverse Events		Throughout the trial					

1. Introduction

1.1 Background

Post-operative infection after lower extremity bypass operations (LEB) can lead to devastating consequences. A systematic review of lower-extremity (LE) re-vascularization cases using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) found that 11.1% of patients were diagnosed with surgical site infections (SSI). [1] Another arterial reconstruction LE randomized control trial (RCT) of 500 patients found a general wound complication incidence rate of 30%, the majority of which were superficial SSIs. [2] Lower extremity bypass (LEB) specific reviews have reported wound complications in as high as 44% of surgical sites (femoral popliteal/tibial and pedal bypasses). [3,4] Another main issue in LEB is swelling, which occurs in about 70% of these patients and leads to increased pressure along the leading edges of often-long wounds. A wide variety of methods to decrease these post-operative consequences are currently part of standard practice. These techniques include covering incision sites with sterile gauze dressing, elevating the leg, and wrapping with pressure dressings. Patients are then instructed to change dressings themselves at home. However, SSI rates demonstrate that these are only partially effective measures, and there remains room to improve post-operative management of infection and swelling.

Negative pressure wound therapy (NPWT), over the past several years, has provided a way to post-operatively manage complex wounds. This is a therapy with potential to decrease rates of SSIs post-LE bypass. Unlike standard gauze dressings, negative pressure wound therapy provides a sealed, moist environment and shuttles fluid away from the wound. A suctioning unit applies even, negative pressure (typically -80 to -120 mmHg) and exudate is suctioned and collected in a control unit. We would like to investigate the efficacy of PICO (Smith&Nephew), a single-use one-step wound dressing which is effective for 7 days. It is lightweight and uses a small hand-held vacuum pump, both of which allow for ease of use. PICO has been FDA-approved.

Case series have been completed to evaluate the efficacy and feasibility of use in orthopedic inpatient and outpatient, community, and vascular surgical wound management [5,6,7,8]. RCT surgical studies have also been performed to compare standard dressings and PICO in caesarean section and elective Crohn's disease and surgery, both reporting a decrease in post-operative wound complications [9,10]. A systematic review of RCTS comparing standard dressings and NPWT in ulcer management and traumatic surgeries found that NPWT is at least as effective, and in cases more effective than gauze dressings. The greatest effectiveness was found in chronic leg and post-traumatic ulcers [11]. However, there remains a lack of evidence on the effectiveness of NPWT in vascular surgery via high-quality randomized control trials. This study aims to bridge that gap.

1.2 Rationale and hypothesis

Lower extremity bypass, a major open vascular surgery, is associated with significant post-operative swelling and infection. This indicates that current therapies, e.g. compression stockings and sterile dressings, are limited in their effectiveness. PICO

single-use negative pressure dressings have been examined in previous studies. However, these were either case series, for chronic wounds, or for non-vascular procedures. The effectiveness of PICO versus standard dressings in LEB has yet to be determined in a prospective, comparative study. Results will indicate whether PICO should be included standard post-operative care of lower-extremity bypass patients. This study is designed to compare PICO and standard care, and determine which offers the best outcomes of decreased days to ambulation and post-operative wound complications.

The study hypothesis is that participants using PICO dressings will demonstrate superior post-operative recovery measures, have reduce leg edema and possibly reduce post-operative surgical site infections.

2. Objectives

These include swelling, infection, and resumption of activities of daily living. Secondary objectives are to (1) compare functional status after 1 year of follow-up and (2) to compare resource utilization associated with treatment of patients randomized to either group.

3. Trial design

This design is a prospective, randomized, two-arm single-center trial comparing the effective of moist gauze dressings to PICO single-use negative pressure dressings.

4. Study population

4.1 Inclusion criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study.

- Age > 35 years old
- Patient to undergo lower extremity bypass using ipsilateral great saphenous vein harvest
- Patient willing to comply with protocol, attend follow-up appointments, complete all study assessments, and provide written informed consent

4.2 Exclusion criteria

- Patients meeting any of the following exclusion criteria are not to be enrolled in the study.
- Life expectancy of less than 2 years
- Any infrainguinal revascularization procedure on index leg within 12 weeks prior to treatment
- Current immune-suppressive medication, chemotherapy, or radiation therapy
- Pregnancy or lactation
- Inability or refusal to provide informed consent
- Patients who received an investigational drug for peripheral arterial disease within 4 weeks of screening or who participated in another non-observational clinical trial in the prior 30 days

- Prior leg bypass on the ipsilateral limb

4.3 Protected populations

- ***Prisoners***
- Due to the complexity of state and federal requirements governing the participation of prisoners in research, patients who are prisoners will not be considered for participation in this trial.
- ***Pregnancy***
- Patients who are known to be pregnant will be excluded from participation. A negative urine pregnancy test is required for all women of childbearing potential prior to starting any study interventions.

5. Trial interventions

The intervention portion of this study is the assignment to regular dressings and PICO negative pressure dressings

5.1 Dressing application

Subjects will be randomized to one of two post-operative wound treatments for LEB – standard gauze dressings or PICO negative pressure wound dressings. Subjects randomized to standard dressings will receive sterile gauze dressings as per standard practice. Subjects randomized to PICO negative pressure dressings will also have these placed in the operating room. Incision sites for both groups will be examined prior to discharge.

5.2 Dressing removal

On day POD 2, patients randomized to the standard dressing group will removal gauze by themselves at home. On POD7, patients randomized to the PICO group will have their dressing removed by a nurse or doctor in clinic. PICO single-use negative pressure dressing is marketed for use up to 7 days.

5.3 Allocation to intervention

Study participants will be randomized via an automatic program in the REDCap database (please see the Repository page for more information about this database). Randomization is instantaneous after pushing a generate button. Study group is automatically recorded in the patient's data. Compared to drawing numbers or encoding information in separate sheets, this eliminates transfer of information between personnel and possibility of miscommunication.

In REDCap, a randomization module is set up as part of the given project. Stratified randomization will be used according to treatment group. Randomization user rights will be granted solely to the Research Coordinator and Research Assistant to minimize investigator bias. If a person is given 'Randomize' privileges, they will be able to view and modify existing data already collected for the randomization strata fields (if stratification is used) when they are performing the randomization.

Since randomization will be performed during the pre-operative period, the patient will be aware of the surgical plan (open vs. endovascular) prior to the date of the surgery. He or she will then have an option to withdraw from the study and choose any appropriate treatment modality, if they so choose.

6. Subject recruitment and consent

6.1 Subject Identification

Eligible patients will be identified by the clinical care team, who will notify a member of the study staff.

6.2 Screening

A member of the study staff will assess patient eligibility using the Preparatory to Research provision, as approved by the institutional review board (IRB). All protected health information used during the screening process of a potential subject will be the minimum necessary for the conduct of this study. Any protected information recorded will be destroyed at the end of the screening process. The clinical care team of the potential subject will be aware of the potential participation in this study as they will be the ones who refer the subject.

For ineligible patients, only the eligibility criteria that were not met (i.e. which criteria excluded the patient from study participation) will be recorded.

6.3 Recruitment and consent

All residents, attending physicians, and research assistants who have undergone training to consent for this project and whose proficiency has been verified will be eligible to consent patients in clinic. After patient has agreed to hear more about the study and has affirmed his/her interest in participating, the consenter will review the consent form. The consenter will answer any questions the patient may have and ask if the patient would still like to participate. The consenter will then ask the patient to sign and date the document. The consenter will sign and date the document. A copy of the form will be made and given to the subject.

7. Activities and measurements

7.2 Data to be recorded at Baseline and Follow-up visits

DEMOGRAPHICS AND MED HIS.	
Age, mean (SD), years	
Race, No. (%)	
	White
	Black
	Hispanic

	Asian/Pacific Islander Native American
Sex, No. (%)	
	Female
	Male
Height, mean (SD) inches	
Weight, mean (SD) pounds	
BMI, mean (SD) kg/m2	
Prior CAD intervention (PTCA/CABG), No. (%)	
DM, No. (%)	
	None
	IDDM
	NIDMM
Renal function, No. (%)	
	Normal
	Renal insufficiency (creatinine >2 mg/dL)
	Dialysis
History of	
	Hypertension, No. (%)
	Myocardial infarction, No. (%)
	Stroke, No. (%)
Laboratory values, mean (SD)	
	WBC, ?109/L
	Hematocrit, %
	Platelets ?109/L
	Glucose, mg/dL
	Creatinine, mg/dL
	Albumin, g/dL
	Hemoglobin A1c, %
	C-reactive protein, mg/L
Medications, No. (%)	
	Aspirin
	ACE inhibitor Antibiotics
	b-Blocker Coumadina
	Low-molecular-weight heparin
	Clopidogrel
	Statin
	Steroids
Smoking status	

OPERATION INDIC. AND CHAR.	
Indication, No. (%)	
	Claudication
	Critical limb ischemia
	Abdominal aneurysm
	Peripheral aneurysm
	Bypass revision
	Other
Procedure side, No. (%)	
	Left
	Right
	Bilateral
Surgical site, No. (%)	
	Femoral above-knee popliteal
	Femoral below-knee popliteal
	Femoral tibial/pedal
	Popliteal tibial/pedal
	Tibial/pedal
	Other
Clean classification, No. (%)	
Sterile preparation solution, No. (%)	
	Betadine based
	Chlorhexidine based
	Other
Estimated blood loss, mean (SD), mL	
Operative time, mean (SD), minutes	
Incision length, mean (SD), cm	
WOUND COMPLICATIONS	
Patients with follow-up	
Worst complication	
	No wound complication
	Other
	Wound dehiscence
	Superficial SSI
	Deep SSI
Any SSI (superficial or deep)	
Any wound complication	
WOUND COMPLIC BY PT. CHAR	
Age	

Race	
	White
	Black
	Other
Sex	
	Female
	Male
BMI	
Prior CAD intervention (PTCA/CABG)	
Abnormal renal function	
History of	
	Diabetes (IDDM or NIDMM)
	Hypertension
	Myocardial infarction
	Stroke
Indication	
	Claudication
	Critical limb ischemia
	Abdominal aortic aneurysm
	Peripheral aneurysm
	Bypass revision
	Other
Surgical site	
	Groin only
	Groin and leg mixed
	All wounds lower than groin
Nonclean classification	
Sterile preparation solution	
	Betadine based
	Chlorhexidine based
	Other
Estimated blood loss	
Operative time	
Total incision length	
Laboratory values	
	WBC
	Hematocrit
	Platelets
	Glucose
	Creatinine
	Albumin

	Hemoglobin A1c
	C-reactive protein
Medication use	
	Aspirin
	ACE inhibitors
	Antibiotics
	b-Blockers
	Coumadinb
	Low-molecular-weight heparin
	Clopidogrel
	Statins
	Steroids

7.3 Baseline

Baseline visit:

- Sign informed consent
- Baseline visit will include standard clinical procedures for PAD patients to undergo lower extremity bypass. Patients will be consented after clinical examination by a surgeon.
- Baseline visit will include a review of past medical history, peripheral vascular history, allergies, and current medications.
- Physical exam will include documentation of blood pressure, heart rate, weight, height, and a full body examination.
- Assessment of cardiology risk stratification and LE symptoms.

7.4 First study mode

Study participants randomized to standard pressure dressings will remove their dressings and replace as necessary on post-operative day (POD) 2. Participants randomized to PICO dressings will have their dressings removed in clinic on POD 7.

For the purpose of this trial, the following data will be collected at scheduled clinic visits (POD 7, POD 14, and POD 30).

- Current signs/symptoms
- Current medications
- Vitals
- Pain scale
- Quality of life questionnaires
- Percent of leg swelling measured 20 cm above and 15 cm below patella

7.8 Data entry

Research affiliates will enter all study data into the REDCap data application within 48 hours of contact with the research subject.

7.9 Subject withdrawals

Subjects may be withdrawn from the study for the following reasons:

- Subject declines further study participation.
- In the investigator's judgment, it is in the subject's best interest.

All protocol-specified visits and follow-up procedures should be performed for every subject enrolled in the trial. If the subject refuses to continue with the study visits, every attempt should be made to continue contact by telephone, written communication, or record review to determine if outcome events have occurred, unless the subject specifically refuses such follow-up. The reason for withdrawal will be documented for all subjects withdrawn from the study. If the withdrawing subject is unwilling to have his/her medical records reviewed until the end of the trial period (to document vital status and cause of death), he/she must submit a written refusal.

7.10 Stopping rules

If a subject is removed from the study due to an SAE, no further subjects will be enrolled at the site until the site's study team has:

1) Assessed the SAE and determined its relationship to the study ("probably related" or "unlikely related"); AND

2) Reviewed the frequency of all SAEs that have occurred at the site

For the study as a whole:
The study intervention will be stopped if any of the below conditions occur:

1) Death of a subject determined to be caused by the study intervention

2) 3 or more subjects experience an SAE

7.11 Investigational Product Accountability

It is the responsibility of the Principal Investigator at this site to ensure the appropriate use and disposition of the supplied PICO negative pressure dressings. A device accountability recording the make, model, and lot number will be maintained by the PI. At the completion of the study, there will be a final reconciliation of dressings used.

8. Data analysis and statistical considerations

8.1 Sample size determination

The estimated average days to complete ambulation is 7 days. In order to detect a significance with estimated 7.5 days (a 7% change) with common SD=0.5 and 85% power, at a p=0.05, we would require 18 subjects. Allowing for a 20% loss of subjects after consent is obtained (due to subjects not meeting clinical stability criteria or because the subject and/or LAR withdrew permission to use data), the study requires a sample size of 22.5 subjects per group. Per funding restrictions for this project (by units provided), we plan to enroll 20 subjects per group, for a total of n=40.

8.2 Analysis of endpoints

This study is intended to compare the post-operative recovery in patients using standard pressure dressings and PICO single-use negative pressure dressings. We will be measuring leg swelling, days to ambulation, and rates of infection. Relevant measurements will be taken at baseline and in subsequence clinical visits on POD 7, 14, and 30. In order to test for significance, we will use a unpaired t-test. An alpha level of 0.05 will determine statistical significance.

9. Risks and benefits of trial participation

9.1 Potential risks

1) As with any patient research, participation in this study poses a risk for breach of confidentiality. RARE

2) Taking part in more than one research study may be harmful to the subject. If subjects are already taking part in another study, we ask that they let us know. Subjects should not take part in more than one study at the same time, unless the subject and the investigators agree that the subject is not likely to be harmed, and the outcome of the study will not be disturbed. RARE

3) Patients may experience discomfort during application of either sterile moist dressings or PICO dressings. This would be on par with standard post-operative protocols LIKELY

4) Dressings may cause irritation of skin and pain upon removal. This is a part of any wound care dressing regimen. LIKELY

5) In rare cases, PICO negative pressure dressings have caused wound complications due to retention of dressing pieces in wounds, in certain cases causing tissue necrosis.

6) Bleeding and resulting death have been reported serious adverse events. Bleeding has been associated with patients who use anti-clotting medication and have received blood vessel grafts in the leg. RARE

7) As with any research study, there may be additional risks of participating that are unforeseeable or hard to predict. RARE

9.2 Mitigation of potential risks

1) To minimize the breach of confidentiality risk, we will not use the subject's name or hospital number to identify them on any non-restricted study records. Instead a unique study number will be assigned to each subject. Access to REDCap will be granted only to study personnel listed on this protocol.

2) Prior to consent for participation in this study, the consenter will discuss with the patient whether or not they are participating in another study. If so, the PI will discuss with the patient in private whether they are likely to be harmed by participating in this study.

3) Application of dressings will be done according to standard clinical care.

4) Removal of dressings will be done according to standard clinical care. Application and removal irritation will be minimized accordingly.

5) The study PI will review with patients the likelihood of these risks prior to and after randomization. If the PI determines that the participant, given their medical and surgical history, is at risk for a serious adverse event, the participant will not be a part of this study.

6) Tissue remnants in wounds (rare) have been largely the result of PICO dressing used individually or in long-term care settings. Patients randomized to the PICO group will have their dressing removed on post-operative day 7 in the vascular surgery clinic. This will be done by a trained nurse, resident, or attending physician.

9.3 Potential benefits and risk-to-benefit ratio

PICO is a potential tool for minimizing post-operative complications, but it has not yet been systematically tested in patients who have undergone lower-extremity bypass operations. The knowledge and insights emanating from this study will potentially advance research efforts surrounding negative pressure wound therapy and PICO single-use dressings. They may also change how we treat post-operative wounds in the future.

Subjects may not receive any direct benefit from participating in this study. The individual has the opportunity to use a potentially more effective wound dressing at no cost to him/her. Additionally, the subject will be contributing to an effort to improve post-operative care of lower-extremity bypass patients. Existing treatment still results in considerable leg swelling and wound complications, and subjects will aid in determining whether PICO is a viable therapy.

All study costs not related to standard clinical care and performed solely for the purpose of research will be paid for by the sponsor.

10. Adverse events and unanticipated problems

10.1 Adverse event definitions

Adverse event (AE)

An adverse event is defined as any untoward or unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Serious adverse event (SAE)

A serious adverse event is defined as any adverse event that meets one of the following criteria: □ Results in death; OR

□ Is life-threatening; OR □ Prolongs hospitalization; OR □ Results in persistent disability; OR □ May jeopardize the subject's health; OR □ May require medical or surgical intervention.

Unanticipated problem (UP) An unanticipated problem is defined as an event that

meets all of the following criteria:

1) Unexpected in severity, nature, or frequency given the research procedures and the characteristics of the subject population (i.e., problems that are not described in this protocol or other study documents); AND

2) Related or possible related to participation in the research; AND

3) Suggests that research places subjects or others at a greater risk of harm related to the research than was previously known or recognized.

10.2 Severity assessment

Sites will assess the severity of all adverse events according to the following scale:

□ Mild = not requiring treatment

□Moderate = resolved with treatment

Severe = inability to carry on normal activities and required professional medical attention

10.3 Causality assessment

The Site PI will determine the relationship of adverse events to the research intervention using the following scale:

□ Definite = AE is clearly related to the study procedures

□ Probable = AE is likely related to the study procedures

□ Possible = AE is possibly related to the study procedures

□ Unlikely = AE is doubtfully related to the study procedures

□ Unrelated = AE is clearly not related to the study procedures

10.4 Procedures for recording and reporting adverse events

- SAE: Any SAE will be reported to the BUMC IRB within 48 hours. DSMC to confirm receipt of notification.
- All SAEs will be included in a report to the BUMC IRB every three months.
- UP: The AE Coordinator will notify the BUMC IRB of all UPs within 48 hours. DSMC to confirm receipt of notification.
- All UPs will be included in a report to the BUMC IRB every three months.
- AE: All other AEs will be reported to the BUMC IRB on a quarterly basis.

11. Administrative requirements

11.1 Good clinical practice

The study will be conducted in accordance with FDA and ICH guidelines for Good Clinical Practice. All study staff will be thoroughly familiar with the contents of this protocol and associated trial materials.

11.2 Data quality assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study subject. Study data will be entered into an electronic case report form (eCRF) by site personnel using a secure, validated, web- based electronic data capture (EDC) application. The coordinating site will have access to all data entry upon entry in the EDC application. Any changes made to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

11.3 Electronic case report form completion

Study sites will be provided with secure access to and training on the EDC application sufficient to permit site personnel to enter or correct information in the eCRFs for the subjects for which they are responsible. ECRFs will be completed for each study subject. It is the investigator's responsibility to ensure the accuracy, completeness, clarity and timeliness of the data reported in the subject's eCRF. The investigator or designated representative shall complete the eCRF as soon as possible after the information is available.

11.4 Study monitoring

Due to financial and staff limitations there are no formal plans to monitor data for this study; however there remains a possibility for this if deemed necessary. All information recorded on the eCRF for this study must be consistent with the subject's source documentation. Should monitoring occur, the study monitor may review protocol compliance, verify eCRFs against source documentation and ensure the protocol is being conducted according to pertinent regulatory requirements. Any review of medical records will be performed in a manner to ensure patient confidentiality is maintained.

11.5 Ethical consideration

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the subjects. The study will only be conducted at sites where IRB approval has been obtained. The protocol, informed consent form, written information given to the patients, safety updates, annual progress reports and any revisions to these documents will be provided to the IRB by the investigator.

11.6 Patient confidentiality

Subject confidentiality of protected health information will be maintained by utilizing secure encrypted database for data collection and transmission with special security provisions in place for subject confidentiality protection. The database will be access on password and login protected computer only in the Department of Surgery with research staff access only.

Study data will contain identifiers (e.g. social security numbers, medical records, date of birth). We will not collect any paper records and only highly secure encrypted electronic REDCap database will be utilized for data collection and transmission. REDCap database

has special provisions in place to ensure security and protection of identifiable research subjects information.

All study data will be kept for three years after completion of the study. All data will be destroyed by deletion from computer files and/or shredding.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

11.7 Investigator compliance

The investigator will conduct the trial in compliance with the protocol approved by the IRB. Changes to the protocol will require written IRB approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects.

11.8 Subject cost and payment

Cost: Subjects will not incur additional costs due to their participation in this study. Study materials will be paid for by the study grant.

Payment: Subjects will not be paid for participation in this study.

12. Funding Sources

This study is funded through an investigator-initiated grant from Smith&Nephew. Solely de-identified data will be viewable to the sponsor.

13. References

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5) Leak K, “A case-series appraisal of a single-use Negative Pressure Wound Therapy system in secondary care”, presented at WOUNDS UK, 2011

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7) A community-based case series appraisal of a single-use Negative Pressure Wound Therapy System, presented at WOUNDS UK, 2012

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9) Pellino et al. “Effects of a new pocket device for negative pressure wound therapy on surgical wounds of patients affected with Crohn's disease: a pilot trial.” Surgical Innovation. 2014. 21 (2): 204-12.

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