Northwell Health

Clinical Trial Protocol

PICO Negative Pressure Wound Therapy in obese women undergoing elective cesarean delivery.

IRB / Protocol Number: 17-0843

National Clinical Trial (NCT) Identified Number: NCT 03414762

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IND/IDE Sponsor: None

Funded by: Department of Obstetrics and Gynecology

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
2.3.1	Updated PICO pump risk regarding magnet	To be consistent with information in the patient brochure.

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Evaluation of the PICO Single Use Negative Pressure Wound Therapy (NPWT) in Obese Women Undergoing Elective Cesarean Delivery.
Study Description:	A randomized controlled, parallel group, superiority, open-label, single-institution, Phase 3 interventional clinical trial to evaluate clinical outcomes in obese gravidas undergoing elective cesarean delivery whose wounds were dressed with the PICO Negative Pressure Wound Therapy (NPWT) versus the standard dressing. We hypothesize that the PICO NPWT will reduce the incidence of surgical site occurrences and interventions and postoperative readmissions in obese women. The study will compare surgical site occurrences and surgical incision intervention incidence within 42 +/- 10 days post cesarean delivery in obese women who have the current standard-of-care dressing versus the PICO NPWT.
Objectives:	The purpose of this study is to compare short-term clinical outcomes among obese women undergoing cesarean delivery between those who received the post-surgical standard-of-care wound dressing versus the PICO negative pressure wound therapy system (NPWT). <u>Primary Objective Measures</u>: The incidence of postoperative Surgical Site Occurrences (SSOs) up to Day 42 (+/- 10 Days) post Cesarean delivery. **SSOs include**: Unanticipated local inflammatory response Prolonged drainage Fluid collection

Dehiscence

Surgical site infection (SSI)

Secondary Objective Measures:

Incidence Rate of Surgical Incision Intervention (SII) up to Day 42 (+/- 10 Days) Post Cesarean delivery.

Interventions include:

Antimicrobials for surgical site infection

Surgical drainage of the incision

Surgical incision packing

Adjunctive negative pressure therapy

Debridement

Re-operation

Endpoints:

Primary Endpoint: confirmed SSO within 42 (+/- 10 Days) post Cesarean delivery.

Secondary Endpoint: confirmed SII within 42 (+/- 10 Days) post Cesarean delivery.

Study Population:

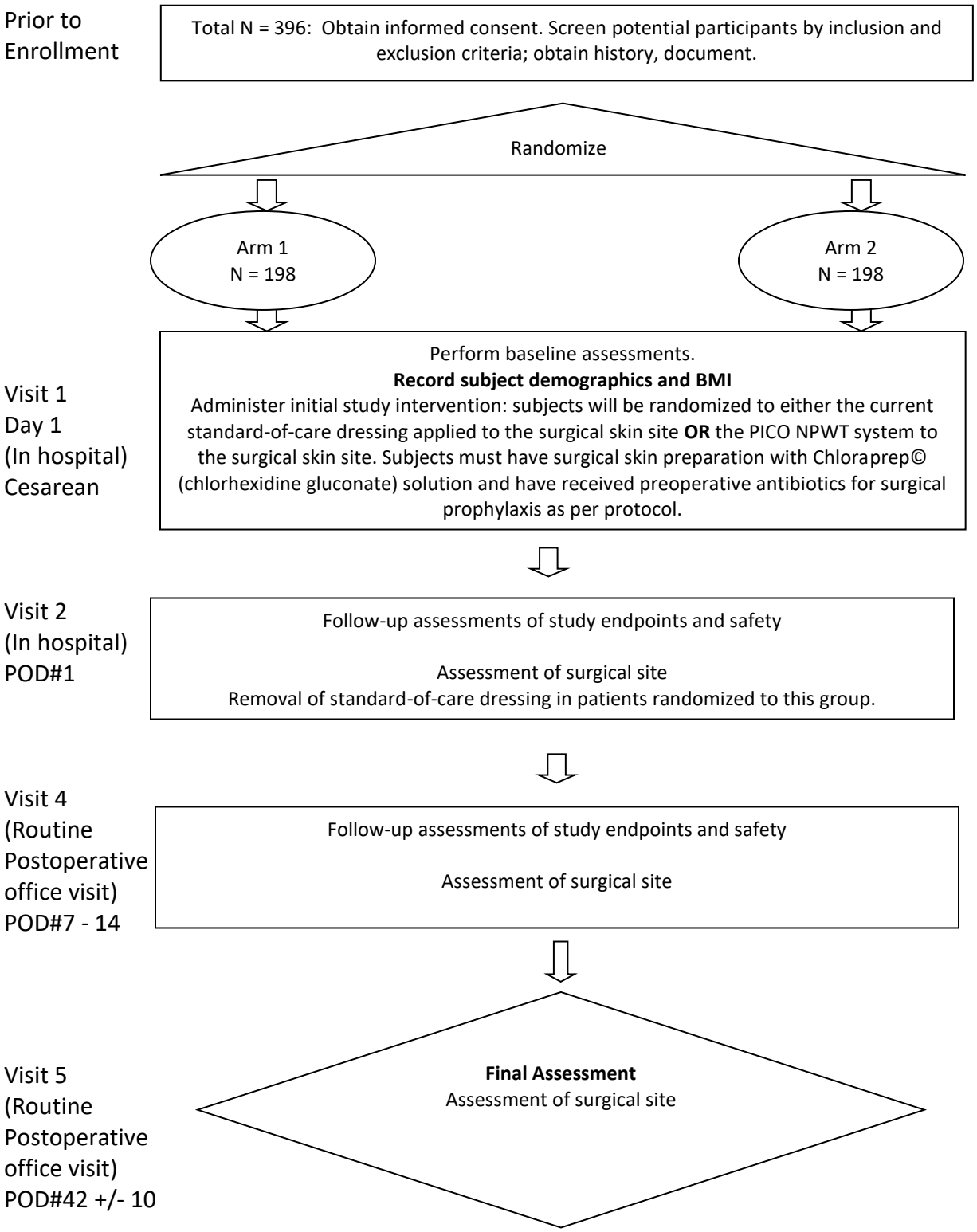
Samples size of 396 females aged ≥ 18 years who are able to provide consent and are undergoing a planned cesarean delivery using subcuticular skin closure technique at the Long Island Jewish Medical Center. Inclusion criteria includes: surgical incision that can be completely covered by the PICO NPWT system, BMI ≥ 35 kg/m^2 in the 42 days prior to surgery, is preoperatively assessed to undergo a procedure with a CDC Wound Classification of I (clean) or II (clean contaminated), and is willing and able to return for all scheduled and required study visits. Patients must have had surgical skin site preparation with chlorhexidine gluconate solution (ChloraPrep©), received preoperative surgical prophylaxis antibiotics as per protocol, and skin must be closed in a subcuticular fashion. Exclusion criteria include delivery for suspected intrauterine infection (defined as maternal fever plus one clinical criteria), diagnosis of systemic or skin infections at time of delivery, critical illness, or high-risk for anesthesia (American Society of Anesthesiologists [ASA] class P4 – P6). Sample size is selected to be 200 participants in the PICO group and 200 participants in a control group that utilizes standard wound dressing technique.

Phase:

3

Description of Sites/Facilities Enrolling Participants:	This study will be performed at a single institution, the Long Island Jewish Medical Center, an 827-bed voluntary, non-profit tertiary care teaching hospital in New Hyde Park, Queens, New York. Patients who present for elective or repeat cesarean delivery who meet eligibility criteria at this institution only will be recruited for participation in the study. The study will not include sites outside of the United States.
Description of Study Intervention:	The PICO Single Use Negative Pressure Wound Therapy Device (Smith and Nephew Healthcare, Hull, United Kingdom) is a non-significant-risk, FDA Class II, medical device commercially available in the USA. The protocol will assess the effectiveness and functional performance of the NPWT system. The PICO unit is a single patient use, battery-powered, disposable unit that can provide continuous 80 - 125 mmHg negative pressure over a total of a 7-day therapy period. It is an easy to use device that also provides audible and visual alerts for low battery, maximum canister volume, and leak conditions. Additional alerts include system error and device life-cycle expiration (8 days). It is contained in a water-resistant housing, which allows the subject to lightly shower with the device. Wound fluids are contained within the 45 mL canister. The dressing is applied to the wound and extra strips are placed over the outside edge to help hold the dressing in place. When the pump is turned on, air is pulled out of the dressing and excess fluid from the wound will start to enter the dressing. The dressing helps to prevent bacteria from entering the wound. It may also improve blood flow to the wound which assists healing. Active Comparator: Standard Dressing Standard-of-care includes coverage of the sutured incision with sterile gauze and non-penetrable barrier (e.g., surgical tape or Tegaderm™) consistent with the national standard for dressing Cesarean delivery incisions. These dressings are removed on postoperative day #1 as per standard protocol.
Study Duration:	We estimate that 8 months will be required to complete the study from when the study opens to enrollment until the completion of data analyses.
Participant Duration:	It will take 42 +/- 10 days for each individual participant to complete all participant visits.

1.2 SCHEMA


Prior to Enrollment
Total N = 396: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Randomize
Arm 1
N = 198
Arm 2
N = 198
Visit 1
Day 1
(In hospital)
Cesarean
Perform baseline assessments.
Record subject demographics and BMI
Administer initial study intervention: subjects will be randomized to either the current standard-of-care dressing applied to the surgical skin site OR the PICO NPWT system to the surgical skin site. Subjects must have surgical skin preparation with Chloraprep© (chlorhexidine gluconate) solution and have received preoperative antibiotics for surgical prophylaxis as per protocol.
Visit 2
(In hospital)
POD#1
Follow-up assessments of study endpoints and safety
Assessment of surgical site
Removal of standard-of-care dressing in patients randomized to this group.
Visit 4
(Routine Postoperative office visit)
POD#7 - 14
Follow-up assessments of study endpoints and safety
Assessment of surgical site
Visit 5
(Routine Postoperative office visit)
POD#42 +/- 10
Final Assessment
Assessment of surgical site

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening/Enrollment/ Baseline Visit 1, Day 1: Cesarean	Study Visit 2 Day 2: Post-Op Day #1	Study Phone Call Post-Op Day 5 – 6 to PICO NPWT Subjects	Study Visit 3 Post-Op Day 7 - 14	Final Study Visit 4 Day 42 +/-10 days
Informed consent	X				
Demographics	X				
Medical history	X				
Randomization	X				
Administer study intervention	X				
Concomitant medication review	X	X		X	X
Physical exam					X
Vital signs	X	X		X	X
Height					
Weight	X			X	X
Incision assessment		X		X	X
Adverse event review and evaluation	X	X		X	X
Assessment of protocol compliance		X	X		
Complete Case Report Forms (CRFs)	X				X

2 INTRODUCTION

2.1 STUDY RATIONALE

Cesarean delivery is the most commonly performed surgical procedure in the United States. Approximately 32% of neonates are born via cesarean delivery. Between 1999 and 2010, the incidence of obesity in the United States increased from 28.4 – 34.0% in women of childbearing age. Obesity contributes significantly to post-surgical complications and any prophylactic measures that can help reduce the incidence of these complications will benefit patient care and outcomes.

This will be a randomized, open-label, single-institution, Phase III, comparative interventional study that aims to determine if the PICO Single Use Negative Pressure Wound Therapy (NPWT) has an effect on incidence of postoperative surgical site complications in patients undergoing cesarean delivery. Subjects will be compared to a control arm treated with a standard-of-care surgical incision pressure dressing. This prospective clinical study will assess the effectiveness and functional performance of NPWT on closed incisions. Clinical outcomes for this study are defined as Surgical Site Occurrences (SSOs) that include unanticipated local inflammatory response, prolonged drainage, fluid collection, dehiscence, and surgical site infection (SSI) as well as Surgical Incision Interventions (SII). This study will compare these outcomes to a control group consisting of Subjects screened for the same inclusion and exclusion criteria but treated with a standard-of-care surgical incision dressing. The NPWT is known to reduce

surgical site infection rates in the general and trauma surgery literature; however, it has not been studied in a large randomized controlled trial in patients undergoing cesarean delivery. A decrease in the incidence of surgical site infections and occurrences in this population could potentially have a major impact in the care of pregnant obese patients undergoing cesarean delivery.

An RCT to evaluate the clinical effect of NPWT in obese women undergoing cesarean delivery is important to provide much-needed evidence in a costly area of healthcare.

2.2 BACKGROUND

Cesarean delivery is the most common surgical procedure performed in the United States. In 2015, the Center for Disease Control (CDC) reported 1,272,503 cesarean births in 2015, resulting in an overall 32.0% cesarean delivery rate. Postpartum surgical site infection (SSI) and wound infections major causes of prolonged hospital stay and causes increased costs to the health care system. SSIs complicate a significant number of patients who undergo cesarean delivery; approximately 18.4% will experience wound infections.

Between 1999 and 2010, the incidence of obesity in the United States increased from 28.4 – 34.0% in women of childbearing age. Obese women have the highest risk of surgical site infection after cesarean delivery even after adjustment for comorbidities including diabetes mellitus. Management of surgical site infection after cesarean delivery can include antibiotics, wound exploration, or surgical debridement. Open surgical wounds may be managed using closure by secondary intention or negative pressure wound therapy. Non-pregnant patients with surgical site infection after laparotomy are managed with closure by secondary intention or the addition of negative pressure wound therapy to the wound; this has been associated with improved healing times compared with allowing closure by secondary intention alone.

There are currently two published trials evaluating post-cesarean surgical site complications in patients who had a cesarean delivery and received either a NPWT dressing versus a standard-of-care pressure dressing. There are several trials that evaluate post-surgical complications in the Trauma, General, and Orthopedic surgery literature.

A randomized controlled trial by Gunatilake RP et al published in April 2017 compared 46 obese patients who were randomized to a NPWT system (the PREVENA Incision Management System manufactured by KCI) to 46 obese patients who were randomized to standard-of-care dressings. The primary endpoints in this study were: unanticipated local inflammatory response, prolonged drainage, fluid collection, dehiscence, and surgical site infection. The secondary endpoints were: incidence of subjects with surgical interventions (antimicrobials, surgical drainage of incision, adjunctive negative pressure evaluation, debridement, or reoperation). Surgical site assessments also included supplementary outcomes of incisional pain scored. This study did not show statistically significant differences between postoperative outcomes in patients who were randomized to the NPWT system versus the standard of care dressing; however, they found a trend towards reduction in incisional wound complications and a statistically significant reduction in postoperative pain scales.

A survey by Searle RJ et al published in August 2017 reported audit data from 399 patients with a BMI ≥ 35 kg/m^2 who used PICO dressings on closed cesarean surgical incisions in Ireland and found that 9% of

these patients developed an SSI, which is less than the previously reported 19.3% in a similar population. In addition, these patients had a much lower readmission rate due to SSI (0.8% versus previously reported 4.3%).

This trial is clinically relevant to address potential prophylactic methods to prevent SSI and SSO in the obese pregnant population. If PICO NPWT contributes to the reduction of SSI and SSO, its use will have a large impact on patient care and a huge cost savings for the health system.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Immediate risks:

The PICO pumps contain a MAGNET. Keep the PICO pumps at least 4 inches (10 cm) away from other medical devices at all times. As with all electrical medical equipment, failure to maintain appropriate distance may disrupt the operation of nearby medical devices.

The first time the PICO pump is turned on, subjects may feel a slight pulling or drawing sensation. In addition, some patients feel discomfort when dressings are changed or removed; however, this discomfort is not expected to be more than the discomfort associated with removal of standard of care dressings.

There is a small risk of skin reddening or sensitization; however, this reaction is not expected to be more frequent than that associated with standard dressings.

Patients may feel embarrassed from being part of a study that is investigating an obese patient population.
Long-term Risks:
There are no known long-term risks associated with the use of PICO dressing.

2.3.2 KNOWN POTENTIAL BENEFITS

NPWT is a non-significant-risk, FDA Class II, medical device commercially available in the USA.

Immediate potential benefits:

An immediate potential benefit of NPWTs is the ease in its application. It provides audible and visual alerts for low battery, maximum canister volume, and leak conditions. There may be a decreased risk of surgical site occurrences, infections, and readmission and reduction in postoperative pain with PICO dressing use.

Long-term potential benefits:

Decreased incidence of surgical site infections and occurrences can benefit patients by reducing long-term wound infections such as delayed closure or healing, need for reoperation for wound closure, pain syndromes, or decreased tensile strength of wounds.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The only potential risk is embarrassment from being in a study that is investigating a potential prophylactic dressing in an obese population. Consent will be obtained discreetly to minimize this risk.

There are minimal risks of participation in this study that far outweigh the value that information regarding a prophylactic dressing could decrease risk of surgical site infection in obese postpartum patients would gain from this study. The PICO dressing is already used by some providers after cesarean delivery and so is considered an option for postoperative care of these patients.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The incidence of postoperative Surgical Site Occurrences (SSOs) up to Day 42 (+/- 10 Days) post Cesarean Section.	The incidence of postoperative surgical site occurrences (SSOs) post Cesarean delivery. SSOs include: - Unanticipated local inflammatory response - Prolonged drainage - Fluid collection- Dehiscence - Surgical site infection (SSI)	A percentage of cesarean deliveries result in SSO leading to prolonged wound healing and postoperative pain, increased rates of secondary infection and re-hospitalization, decreased patient satisfaction, and increased costs of medical care. NPWT has been shown to decrease rates of postoperative infection and wound dehiscence in a non-obstetrical population.
Secondary		
Incidence Rate of Surgical Incision Intervention (SII) up to Day 42 (+/- 10 Days) Post Cesarean delivery.	Incidence rate of surgical incision intervention (SII) post Cesarean delivery. Interventions include:	These interventions are costly to the healthcare system and reduce quality of care

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	- Antimicrobials for surgical site infection - Surgical drainage of the incision - Surgical incision packing - Adjunctive negative pressure therapy - Debridement - Re-operation	and decrease patient satisfaction. Interventions that can prevent these necessary procedures are important to justify.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Hypothesis: We hypothesize that the PICO NPWT dressing will decrease the incidence of surgical site infections and occurrences in patients with a BMI ≥ 35 kg/m^2 undergoing cesarean delivery.

Trial phase: 3

Description of trial design: A randomized, controlled, single-institution, interventional clinical trial to evaluate clinical outcomes.

Methods used to minimize bias:

Selection bias will be minimized by reducing the exclusion criteria to include all eligible subjects. Also, the randomization sequence will be concealed from investigators at the time of obtaining consent from the trial participants.

There will be no blinding in the study. Neither the participants nor the physicians will be blinded to the study treatment they are randomized to.

Masking or blinding is not feasible in this study because the size, shape, and components of the PICO and standard dressings are different as is the length of time each dressing is worn. However, participant ascertainment biased will be minimized because diagnosis of an SSO/SSI and need for SII will be made and determined by skilled resident and attending physicians at each of the routine visits, not by patient report. Co-intervention bias will be minimized because there will be no changes in routine post-operative or nursing care instructions between groups.

The statisticians who are responsible for analyzing the results will not be made aware which group received the PICO NPWT dressing versus the standard wound dressing.

Recruitment bias will be minimized by ensuring that all participants who meet inclusion and exclusion criteria with a planned cesarean delivery during the specified time frame are approached and offered participation in the study. Most hospitals utilize standard of care wound dressings similar to the dressing described for the standard dressing group in this proposal, which will minimize clinical practice bias.

Number of study groups/arms: There will be two study groups, Group 1 will be randomized to receive the standard of care pressure dressing and Group 2 will be randomized to receive the PICO NPWT dressing postoperatively.

Study intervention duration: The study period will begin with the day of the scheduled cesarean delivery procedure and end 42 +/- 10 days postoperatively.

Name of study intervention: The Smith & Nephew PICO single-use negative pressure wound therapy system.

Planned interim analysis: There are no planned formal interim analyses.

Stratification: Subjects will be stratified and sub-analyses performed by BMI: 35 – 39.9 kg/m^2, 40 – 44.9 kg/m^2, 45 – 49.9 kg/m^2, 50 – 54.9 kg/m^2.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The control group will be randomized to receive the standard-of-care pressure dressing that includes coverage of the sutured incision with sterile gauze and non-penetrable barrier (e.g., Tegaderm™) consistent with the national standard for dressing Cesarean section incisions. These dressings are removed on postoperative day #1 as per standard protocol.

The control dressing will be the current standard of care pressure dressing that is used on all patients undergoing cesarean delivery. There are no known or potential problems associated with the control group. All other interventions will be as per current protocol.

The study design is a superiority randomized controlled trial (RCT) because the aim is to show that the PICO NPWT is superior to the standard pressure dressing in regards to incidence of SSIs and SSOs.

4.3 JUSTIFICATION FOR DOSE

Not applicable.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

We will recruit obese women undergoing elective cesarean section. Subjects who consent will be randomized to use either the PICO NPWT or standard of care dressing.

Females aged ≥ 18 years with BMI ≥ 35 kg/m^2 who are able to provide consent and are undergoing a planned cesarean delivery using subcuticular skin closure technique at the Long Island Jewish Medical Center.

Screening procedures will not be performed under a separate screening consent form.

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study; willing and able to return for all scheduled and required study visits
3. Female, aged 18 – 55 years
4. BMI ≥ 35 kg/m^2 in the 42 days prior to surgery
5. In good general health as evidenced by medical history with a 24 – 41 weeks gestational age pregnancy scheduled for cesarean delivery for any routine indication (repeat procedure, breech presentation, abnormal placentation, uterine anomaly, maternal medical condition, or elective)
6. Ability to and willingness to adhere to the PICO negative pressure wound therapy regimen
7. Surgical skin site preparation with chlorhexidine gluconate solution (ChloraPrep©)
8. Received preoperative surgical prophylaxis antibiotics as per protocol
9. Surgical incision that can be covered completely by the NPWT skin system
10. Pre-operatively assessed to undergo a procedure with a CDC Wound Classification of:
    a. Class I (Clean): An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered
    - OR -
    b. Class II (Clean Contaminated): An operative wound in which the respiratory, alimentary, genital, or uninfected urinary tract are entered under controlled conditions and without unusual contamination
11. Wound hemostasis has been achieved

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Cesarean delivery before fetal viability (24 0/7 weeks gestational age)
2. Unplanned Cesarean delivery

3. Fetal death
4. Known allergic reactions to components of the PICO NPWT system
5. Systemic bacterial or fungal infection at the time of surgery
6. Diagnosis of systemic or remote-site skin infections at time of delivery
7. Treatment with another investigational drug or other intervention within 7 days prior to cesarean delivery or 42 +/- 10 days after cesarean delivery
8. Delivery for suspected intrauterine infection (defined as maternal fever plus one clinical criteria)
9. Critical illness or immune-compromising disease (eg acquired immunodeficiency syndrome)
10. Chronic steroid use
11. Pre-operatively assessed to have a CDC Wound Classification of:
    - Class III (Contaminated): Open, fresh, accidental wounds, and/or major breaks in sterile technique or gross spillage from the gastrointestinal tract
      - OR -
    - Class IV (Dirty-Infected): Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera
12. High-risk for anesthesia (American Society of Anesthesiologists [ASA] class P4 – P6)
13. Intra-operative hemorrhage requiring blood transfusion, disseminated-intravascular coagulopathy (DIC) or any other medical or surgical condition during the Cesarean section deemed by the investigator to pose a prohibitively high risk for surgical re-exploration
14. Life expectancy of < 12 months
15. Unable to speak or understand English, with no interpreter available

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this trial (screen failure) because of an early delivery or delivery at a time other than their scheduled delivery time may be rescreened but cannot participate in the study. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Potential study participants will be approached by study personnel at time of presentation for her scheduled cesarean delivery at Labor and Delivery at the Long Island Jewish Medical Center.

There are approximately 1 – 2 scheduled cesarean deliveries per day between the Ambulatory Care Clinic, Garden City OBGYN (Long Island Jewish Medical Center/Northwell Health OB/GYN practice) and the Women's Comprehensive Care Center (Long Island Jewish Medical Center Faculty practice). Approximately 34% of these patients are obese. We anticipate a 75% accrual rate.

Patients will be identified and approached while they are waiting for cesarean delivery surgery time by study personnel. Study personnel will show the patients an example of a PICO dressing and a standard of care dressing and explain study protocol and procedures.

A pregnant participant population must be used as subjects in this study because the primary endpoint is SSO and SSI incidence in patients who are undergoing cesarean delivery.

Participants will not be compensated for participation in the study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The PICO Single Use Negative Pressure Wound Therapy Device (Smith and Nephew Healthcare, Hull, United Kingdom) is a non-significant-risk, FDA Class II, medical device commercially available in the USA. The PICO unit is a single patient use, battery-powered, disposable unit that can provide continuous 80 - 125 mmHg negative pressure over a 5 to 7-day therapy period. It is an easy to use device that also provides audible and visual alerts for low battery, maximum canister volume, and leak conditions. Additional alerts include system error and device life-cycle expiration (7 days). It is contained in a water-resistant housing, which allows the subject to lightly shower with the device. Wound fluids are contained within the 45 mL canister.

The dressing is applied to the wound and extra strips are placed over the outside edge to help hold the dressing in place. When the pump is turned on, air is pulled out of the dressing and excess fluid from the wound will start to enter the dressing. The dressing helps to prevent bacteria from entering the wound. It may also improve blood flow to the wound which will help it to heal.

The standard-of-care is consistent with the national standard for dressing Cesarean section incisions and includes, but not limited to, coverage of the sutured incision with sterile gauze and non-penetrable barrier (e.g., Tegaderm™). The non-penetrable barrier may be left in place for a minimum of 1 day and no longer than 2 days (± 4 hours) to promote epithelialization of the surgical incision edges. After the dressing is removed, the surgical site is left exposed to air to promote further healing. Other therapies include traditional gauze dressings with or without advanced therapies such as hydrocolloids, growth factors, and Negative Pressure Wound Therapies.

6.1.2 DOSING AND ADMINISTRATION

The PICO dressing provides 80 - 125 mmHg negative pressure over a 5 day therapy period as a standard setting and this will be used in all patients.

Patients will be taught how to remove the dressing at home after the total 5-day period. Dressing removal is not difficult and should not cause excess pain or discomfort. In order to remove the dressing, the pump is disconnected and the dressing is removed by gently pulling the adhesive edges. The entire dressing and pump can be disposed of in the garbage.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The PICO dressing and supplies for the pressure dressing are available on the Long Island Jewish Medical Center Labor and Delivery Unit. Study personnel will obtain dressing and apply dressing.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The Smith and Nephew PICO device (Figure 1) is packaged for single use and does not need returning or sterilization. The battery pack retains its charge for 7 days delivering a continuous negative pressure. The dressing is designed in 4 layers: top film layer with a high moisture vapor transmission rate (MVTR) allows one-way transpiration of exudate vapor, proprietary absorbent layer moves exudate away from the wound and initiates evaporation, airlock layer maintains open airflow and allows even distribution of negative pressure across the dressing, and the wound contact layer is composed of silicon and does not lead to in-growth of granulation tissue into the dressing material to decrease pain with removal. The pump is a water-resistant, quiet, pocket-sized, canister-free system that uses two AA lithium batteries that last for the 5 – 7 day therapy. The device is packaged in a disposable cardboard box (Figure 2) and can be kept at room temperature. PICO™ is supplied in a pack that can be taken off the shelf when required. It contains a single use pump, which lasts for 7 days and two individually packed dressings and fixation strips (allowing for the wound to be inspected during those 7 days).

PICO specifics from manufacturer product safety data sheet:
Dressing: Laminate of silicone/acrylic adhesive coated polyurethane films to polyethylene layer and polyacrylate/cellulose airlaid layer. A polyurethane port and an acrylic copolymer/nylon filter membrane are bonded to the laminate using acrylic adhesive. PVC tubing is also bonded to the polyurethane port using an acrylic adhesive. Laminate is placed on HDPE handles.
Secondary fixation strips: Laminate of acrylic adhesive coated on polyurethane film placed between polyethylene, polypropylene and paper carriers.
Pump: Internal components consist of PCBA (Printed Circuit Board Assembly consisting of multiple electronic components, PCB and soldered joints), electric motor driven diaphragm pump, air manifold (thermoplastic elastomer), wiring, connections and steel battery contacts. External components consist of 2 case halves (ABS thermoplastic), air inlet connection (ABS thermoplastic), button (thermoplastic elastomer), lenses (polystyrene) and battery cover (ABS thermoplastic).

A 10 x 30cm PICO dressing size fits most cesarean section incisions, and larger and smaller sized dressings are available.

The standard pressure dressing is composed of Telfa®, a non-adherent wound dressing which consists of absorbent cotton fibers impregnated with polyhexamethylene biguanide enclosed in a sleeve of thermoplastic polymers, cotton 4” x 4” sterile mesh gauze manufactured by Medronic (Minneapolis, MN, USA) and a non-penetrable barrier (e.g., tape or Tegaderm™ adhesive film (3M, USA).

Figure 1:

Figure 2:

6.2.3 PRODUCT STORAGE AND STABILITY

Both the standard dressing supplies and the PICO dressing can be stored in the operating room storage units. Both must be stored in a cool, dry place <25°C and kept away from sources of ignition and strong light sources.

6.2.4 PREPARATION

Both dressing are easily applied in a few minutes. There is no required thawing, diluting, mixing, reconstitution/preparation, or difficult assembly.

How to apply instructions from PICO package insert:

Application
1. Remove any excess hair to ensure close approximation of the dressing to the wound. If necessary, irrigate the wound with sterile saline and pat the wound dry.

2. Using a clean technique, peel off the central release handle and place the dressing centrally over the wound to reduce the chance of wound fluid coming into contact with the port. The port should be uppermost from the wound (depending on the patient's primary position), placed on intact skin and not extend over the wound to prevent fluid pooling around the port and blocking the negative pressure. Remove the other two

handles and smooth the dressing around the wound to prevent creasing. Reposition if required to ensure border is not creased.

3. Once the dressing is in place, remove the pump and the batteries from the tray. Insert the batteries. Replace the cover. Following this all three lights should flash once.

4. Join the pump to the dressing by twisting together the tubing connectors. Press the orange button to start the application of negative pressure. The green light will start to flash indicating the system is working properly.
Depending on the size of the wound, the pump should take up to 30 seconds to establish negative pressure wound therapy.

5. If using SKIN-PREP™ prior to application of the fixation strips (see Precautions), wipe the area surrounding the dressing and allow skin to dry.

6. Apply the fixation strips to each of the four sides of the dressing. Remove top carrier on the strip after each one has been applied. These strips maintain the seal over the wear time of the dressing. In awkward areas, it may be useful to apply the strips to help achieve a seal prior to switching on the pump. Place each strip so that it overlaps the dressing border by approximately 1cm (2/5in.). Ensure tubing is not twisted or trapped between clothing.
Please note that if at any time the fixation strips are removed, the dressing should also be replaced.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This trial tests a clinical intervention that is not amenable to protection against performance bias through the blinding of participants, clinical staff or data collectors. There will be no blinding in the study. Neither the participants nor the physicians will be blinded to the study treatment they are randomized to.

The Biostatistics Unit at the Feinstein Institute for Medical Research [BU-FIMR] will develop a randomization plan for the study using the Biostatistics Randomization Management System [BRMS]. BRMS is a secure, HIPAA-compliant, web-based application that allows investigators to randomize subjects into randomized clinical trials (RCTs) using a personal computer with internet access. The BRMS allows for multi-center, stratified, and single/double blinded RCTs. Randomization notifications are automatically sent to the PI and other authorized personnel. BRMS maintains compliance in RCTs.

A randomization schema will be generated by the BU-FIMR using the method of permuted blocks. Subjects will be randomly assigned in a 1:1 ratio to either ‘PICO’ or ‘STANDARD DRESSING’. Details of the randomization procedure, including required record keeping will be further developed upon approval of the protocol.

The RA will randomize participants in the operating room at the start of their cesarean procedure and advise the operating obstetrician and nursing staff of the allocated treatment as close to the end of the procedure as possible in order to minimize performance bias.

To minimize the potential for outcome detection bias, an expert statistician, blinded to group allocation, will assess the data to determine the primary outcome.

Subjective outcomes (SSI/SSOs) are reported by patients or observed by study personnel, who cannot be blinded because they need to check the dressings.

Outcome assessors will be masked to allocation.

6.4 STUDY INTERVENTION COMPLIANCE

In order to complete the study intervention, the participant must have worn the PICO NPWT dressing for a minimum of 5 days after surgery. On the fifth postoperative day, the participant may remove the dressing at home. A phone call to each participant randomized to the PICO NPWT dressing will be made on the 5th or 6th postoperative day (after discharge to the hospital) to verify compliance with the use of the device. No documents are mandatory for the participants to complete and adherence to the protocol will be verified by patient report only.

6.5 CONCOMITANT THERAPY

Not applicable.

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from PICO dressing compliance before a minimum of 5 days does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason the PICO dressing was discontinued:
  - Patient discomfort,
  - Misunderstanding of use,

  - Loss of supplies,
  - etc.
- Incision assessment
- SSI or SSO

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- The PICO device is not compatible with MRI and cannot be taken in to an MRI suite. If the patient requires MRI, the PICO dressing will need to be discontinued

The reason for participant discontinuation or withdrawal from the study will be recorded. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 10 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Screening procedures and evaluations may be performed on the day of enrollment but no more than 10 days prior to the day of enrollment. The screening process will be a discussion with the patient and review of medical history and height and weight to determine eligibility, and explanation of the study rational and study protocol, and demonstration of the two dressing options. Informed consent will then be obtained and patients will have the opportunity to ask questions.

The study intervention will be administered at the end of the scheduled cesarean delivery procedure. Standard dressings will be removed on postoperative day 1 as per current protocol and PICO NPWT dressings will be changed if necessary in the hospital and removed on postoperative day 5 by the patient at home.

Procedures that will be completed during the study as part of regular standard of clinical care: the post-operative visits on day 7 – 14 and 42 +/- 10 days are part of regular standard of clinical care and the outcomes and incision assessments after the participating patients leave the hospital will be performed by skilled residents and attending physicians at these visits. Charts will be reviewed to ascertain if SSO/SSIs were diagnosed or SIIs were necessary.

During these regularly scheduled visits, a **physical examination and incision assessment** will be performed including weight, abdominal exam, incision exam, and all regular postoperative visit exams including breast and pelvic (at the 42 +/- 10 day visit only) as part of the routine standard of care.

If follow-up visits or unscheduled visits are required for treatment of SSO/SSIs or SIIs, information regarding the type of SSO or SII required will be obtained from review of the medical chart.

Surgical Site Occurences include: unanticipated local inflammatory response, prolonged drainage, fluid collection, dehiscence, surgical site infection (SSI). SSI is diagnosed using the following criteria: warmth to touch, pain with palpation, skin redness, irritation, or induration, large amount of drainage or purulent drainage, fluctuance suspicious for wound abscess, fever, and/or wound odor.

Surgical Site Interventions include: Antimicrobials for surgical site infection, surgical drainage of the incision, surgical incision packing, adjunctive negative pressure therapy, debridement, or re-operation.

Information that will be obtained through review of existing data:

- Age
- BMI (kg/m^2)
- Medical comorbidities
- Pregnancy history (term, preterm, abortions, and living history)
- Mode of prior deliveries, if applicable
- Indication for cesarean delivery
- Incision assessment information from residents and attendings at follow-up visits.

8.2 SAFETY AND OTHER ASSESSMENTS

Sequence of events that will occur during screening process:

1. Review of scheduled cesarean delivery schedule for the day.
    a. Screening procedures must be performed within 10 days of study enrollment.
2. Review of medical charts to assess for eligibility (see below).
3. Approach patient and explain trial and interventions.
4. No dietary or activity considerations are required for participation in the trial; however, patients will be counseled that the PICO dressing protocol requires the dressing to be in place for a minimum of 5 days.
5. Assessment of ability to comply with study intervention.
6. Obtain consent.
7. The patient will not be randomized until presentation to labor and delivery and randomization group will not be exposed to healthcare team until as close as possible to the end of the surgical procedure.

Information that will be obtained through review of existing data (i.e. patient's medical chart):

- Age
- BMI (kg/m^2)
- Medical comorbidities
- Pregnancy history (term, preterm, abortions, and living history)
- Mode of prior deliveries, if applicable
- Indication for cesarean delivery
- Incision assessment information from residents and attendings at follow-up visits

No study specific procedures will be performed and so no results will be provided to patients.

List and description of the following procedures/evaluations, as applicable:

- **Physical examination**: height and weight, fundal height, fetal heart rate measurement (initial study day prior to administration of intervention, and incision assessment).
- **Vital signs**: temperature, pulse, and blood pressure.
- **Assessment of adverse events.** Adverse events will be followed by attending physicians and research PI Anar Yukhayev, MD. There are minimal expected adverse events that are not beyond the potential adverse events that could occur from the regular standard dressing (i.e. dressing tape site reaction or allergy to tape)

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

OR

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the

study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

Anar Yukhayev, MD will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Anar Yukhayev, MD will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Anar Yukhayev, MD will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

Not applicable.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 30 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 30 days of of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 30 days of the IRB's receipt of the report of the problem from the investigator.

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under

812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

The Smith and Nephew PICO NPWT dressing is superior to the standard cesarean incision dressing in preventing surgical site occurrences.

Null: The Smith and Nephew PICO NPWT dressing is NOT superior to the standard cesarean incision dressing in preventing surgical site occurrences.

- Secondary Efficacy Endpoint(s):

The Smith and Nephew PICO NPWT dressing is superior to the standard cesarean incision dressing in preventing surgical site infections.

Null: The Smith and Nephew PICO NPWT dressing is NOT superior to the standard cesarean incision dressing in preventing surgical site infections.

9.2 SAMPLE SIZE DETERMINATION

- Outcome measure used for calculations (almost always the primary variable): incidence of surgical site occurrences.
- Type I error rate (alpha): 0.05 (5%)
- Power level: 80%

Based on results from several clinical studies and the American Congress of OBGYN Practice Bulletin on Obesity in Pregnancy, we estimate the proportion of subjects with surgical site occurrences among obese women who undergo elective cesarean surgery to be about 18%. We accept that an absolute difference between study groups of 10%, will be a clinically meaningful difference. Therefore, a chi-square test will yield 80% power to detect a clinically important difference of 10% between study groups (SOC proportion of 18% vs. PICO NPWT proportion of 8%, an odds ratio of 0.396) when the sample size

in each group is 180 *evaluable* subjects. Assuming an attrition rate of about 10%, we would need to recruit about 200 subjects per group (180/0.90=200 subjects).

Note: A study participant is considered 'evaluable' if she has completed all phases of the study including the last visit of the last scheduled procedure in the schedule of activities, i.e. the final study visit 4—day 42±10 days post-op.

9.3 POPULATIONS FOR ANALYSES

The primary statistical analysis will be based on a modified intention-to-treat (participants who underwent surgery and received the intervention). All subjects will be analyzed according to the intention-to-treat [ITT] principle. A patient will be considered evaluable and will be included in the intention-to-treat analysis if the patient has completed all phases of the study including the last visit of the last scheduled procedure in the schedule of activities, i.e. the final study visit 4—day 42±10 days post-op. Analyses that take into account the actual treatment received (e.g. use of PICO NPWT dressing for a minimum 5 days) will be carried out as a secondary analysis (per protocol [PP] analysis).

This was chosen to avoid various misleading artifacts that can arise in intervention research such as non-random attrition of participants from the study or crossover. Subjects strayed from the protocol (for instance, by not adhering to the prescribed timing of intervention, or by withdrawing from the study) will still be analyzed in the group to which they were assigned. We want to estimate the effects of using a PICO dressing at all in practice, not the effects in the subgroup of the participants who adhere to it. If patients receive a different type of dressing (intervention) accidentally from the one they were assigned, they will be excluded from the study in order to remove any bias that could arise from reasons why a provider chose to use that specific dressing instead of the assigned dressing.

In addition, a per-protocol analysis dataset will be analyzed (entire control group and PICO group who used the PICO NPWT dressing for a minimum of 5 days.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Descriptive statistics (e.g. means, standard deviations or medians and interquartile range for continuous data; frequencies and percentages for categorical data) will be calculated for the patients who meet the final inclusion/exclusion criteria.

For descriptive purposes, the overall crude estimates of the incidence of any SSO or any SII will be calculated. These incidences will also be expressed per 100 or 1,000 or 10,000 patients. The chi-square test or Fisher's exact test will be used to compare the crude incidence rates of any SSO or any SII between study groups (NPWT vs. SOC).

For continuous and ordinal variables, data will be expressed as a median with interquartile range. For dichotomous variables, percentages will be calculated. Comparisons will be performed with the Mann-Whitney test for continuous variables as appropriate. Comparisons of percentages will be performed with the Fisher Exact test as appropriate.

The incidence of SSI and SSO per 100 patients between groups will be compared. Risk ratios (RR), 95% CIs and p values assuming a 5% significance level will be presented.

For the primary outcome, the number needed to treat and absolute risk reduction will be calculated from the RR. While we do not anticipate differences between groups in terms of known or unknown prognostic factors because of randomization, adjusted analyses using multivariate logistic regression models will be used if any difference in prognostic variables is detected.

Covariates will be prespecified:

- Medical comorbidities
    - Hypertension (pregestational and gestational)
    - Diabetes (pregestational and gestational)
    - HIV
- Smoking status
- Prior cesarean delivery
- Steroid exposure (betamethasone) within 2 weeks of surgery
- Need for preoperative hair removal (particularly shaving)

Checks of assumptions (e.g., normality) underlying statistical procedures will be performed and whether any indicated corrective procedures will be applied (e.g., transformation or nonparametric tests).

A mixed model approach (generalized linear mixed model [GLMM]) will be used to examine the incidence of SSOs and SIIs (separately) between study groups, and other factors of interest such as medical comorbidities (Hypertension, Diabetes, HIV status), smoking status, prior cesarean delivery, steroid exposure within 2 weeks of surgery, and need for preoperative hair removal. Adjusted Incidence Rate Ratios [IRR] and their associated confidence intervals will be obtained from this approach.

If feasible, a sub-analysis will be performed according to the following BMI stratification of the study participants: 35 – <40 kg/m^2, 40 – <45 kg/m^2, 45 – <50 kg/m^2, ≥50 kg/m^2.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Primary endpoint: the incidence of postoperative surgical site occurrences (SSOs) post cesarean delivery. SSOs include:

- Unanticipated local inflammatory response – measured by redness, tenderness, warmth, or induration on exam. This is a binary nominal categorical variable that will be measured as a repeated measure.

- Prolonged drainage – measured as drainage from surgical skin site ≥3 days from time of surgery. This is a binary nominal categorical variable that will be measured as a repeated measure.
- Fluid collection – measured as need for skin opening to drain fluid collected (seroma) underneath the skin wound. This is a binary nominal categorical variable that will be measured as a repeated measure.
- Dehiscence – measured as opening of skin wound ≥ 2mm. This is a binary nominal categorical variable that will be measured as a repeated measure.
- Surgical site infection (SSI) - measured by redness, tenderness, warmth, or induration on exam with subject fever or purulent drainage. This is a binary nominal categorical variable that will be measured as a repeated measure.

The results of statistical procedure(s) will be presented as odds ratios with 95% confidence intervals, and number-needed-to-treat.

Missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, nonadherence and lost to follow-up by reporting this data as missing (and the reason why) and including all available data in the analysis.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoint: Incidence rate of surgical incision intervention (SII) post Cesarean delivery. Interventions include:

- Antimicrobials for surgical site infection. This is a binary nominal categorical variable that will be measured as a repeated measure. Analysis of this secondary endpoint is dependent on findings of primary endpoints.
- Surgical drainage of the incision. This is a binary nominal categorical variable that will be measured as a repeated measure. Analysis of this secondary endpoint is dependent on findings of primary endpoints.
- Surgical incision packing. This is a binary nominal categorical variable that will be measured as a repeated measure. Analysis of this secondary endpoint is dependent on findings of primary endpoints.
- Adjunctive negative pressure therapy (i.e. need for wound vac therapy). This is a binary nominal categorical variable that will be measured as a repeated measure. Analysis of this secondary endpoint is dependent on findings of primary endpoints.
- Debridement. This is a binary nominal categorical variable that will be measured as a repeated measure. Analysis of this secondary endpoint is dependent on findings of primary endpoints.
    - Re-operation. This is a binary nominal categorical variable that will be measured as a repeated measure. Analysis of this secondary endpoint is dependent on findings of primary endpoints.

The results of statistical procedure(s) will be presented as odds ratios with 95% confidence intervals, and number-needed-to-treat.

Missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, nonadherence and lost to follow-up by reporting this data as missing (and the reason why) and including all available data in the analysis.

9.4.4 SAFETY ANALYSES

Safety endpoints will be analyzed as summary statistics during treatment.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

The following demographic data will be collected for descriptive statistics and will be compared between groups using inferential statistics:

- Age
- Race
- Ethnicity
- Gravidity/Parity
- Prior Cesarean delivery
- Gestational age (weeks)
- BMI (kg/m^2)
- Indication for cesarean delivery
- Medical comorbidities
    - Hypertension (pregestational and gestational)
    - Diabetes (pregestational and gestational)
    - HIV
- Smoking status
- Steroid exposure (betamethasone) within 2 weeks of surgery
- Need for preoperative hair removal (particularly shaving)

9.4.6 PLANNED INTERIM ANALYSES

There are no planned formal interim analyses.

9.4.7 SUB-GROUP ANALYSES

Sub-group analysis based on demographic data such as age, sex, or race are not warranted. This study intervention is only meant for use in a population of reproductive-age women undergoing cesarean delivery for this purpose.

Sub-group analysis will be performed by BMI: 35 – 39.9 kg/m^2, 40 – 44.9 kg/m^2, 45 – 49.9 kg/m^2, 50 – 54.9 kg/m^2.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Data will be collected at baseline, and participants followed up on the first and postoperative day, the PICO group will be telephoned on postpartum day 5 or 6, and then at two postpartum visits: the 7 – 14 day incision check and the 6-week postpartum visit.

9.4.9 EXPLORATORY ANALYSES

Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol:

Informed consent document attached to this IRB submission.

Smith & Nephew PICO Patient Information:

https://www.smith-nephew.com/global/assets/pdf/products/wound/31447%20uk%20pico%20patient%20info%20leaflet.pdf

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records.

The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <study participants, investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in the RedCap (Nashville, Tennessee) database. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived in the RedCap (Nashville, Tennessee) database.

This study is not funded by the NIH.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Not applicable.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Anar Yukhayev, MD	Gary Goldberg, MD
Long Island Jewish Medical Center	Long Island Jewish Medical Center
270-05 76th Ave, Queens, NY 11040	270-05 76th Ave, Queens, NY 11040
718-470-7660	718-470-7660
AYukhayev@northwell.edu	ggoldberg2@northwell.edu

10.1.6 SAFETY OVERSIGHT

Safety oversight will not be under the direction of a Data and Safety Monitoring Board (DSMB) because this study is minimal risk.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Anar Yukhayev MD and Gary Goldberg MD will conduct on-site monitoring, throughout the study, and a targeted or random review of certain data (targeted data verification of endpoint and safety and other key data variables).
- The data will be reviewed in aggregate for data safety monitoring every 30 days.
- Independent audits will not be conducted to ensure monitoring practices are performed consistently across all participating sites.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into <specify name of data capture system>, a 21 CFR Part 11-compliant data capture system provided by the <specify Data Coordinating Center>. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 15 working days of identification of the protocol deviation, or within 15 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the IRB. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 10 years after the completion of the primary endpoint by contacting Anar Yukhayev, MD.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with Northwell Health has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure

UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
v.1.1	1/12/2018	Statistical Considerations	Please see modifications in attached **PACHTMAN_RCT_STATREVISE_2018_JAN_11.docx**

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