2021

Preventing Adverse Incisional Outcomes at Cesarean Multicenter Trial

PREVENA – NCT03009110

PROTOCOL AND STATISTICAL ANALYSIS PLAN

Prophylactic Negative Pressure Wound Therapy in Obese Women at Cesarean: a Multicenter Randomized Trial

Short Title: Preventing Adverse Incisional Outcomes at Cesarean Multicenter Trial

Acronym: "Prevena-C Multicenter Trial"

STUDY PROTOCOL

Version 1.9

Date: August 29, 2019

Funding Agency: National Institute of Child Health and Human Development

Principle Investigator: Methodius G. Tuuli, MD, MPH

Study Sites:

Clinical Coordinating Center	Indiana University PI: Methodius Tuuli, MD, MPH (Steering Committee Chair)
Data Management Center	Washington University in St Louis Co-I: Esther Lu, PhD (Study Statistician)
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Study Site #3	University of Alabama at Birmingham Site PI: Lorie Harper, MD, MSCI Co-I: Alan Tita, MD, PhD
Study Site #4	Ochsner Medical Center Site PI: Sherri Longo, MD
Study Site #5	Mercy Hospital in St Louis (Closed) Site PI: Amanda Trudell, MD, MSCI
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PROTOCOL SUMMARY

Prophylactic Negative Pressure Wound Therapy in Obese Women at Cesarean: a multicenter Randomized Trial (Prevena-C Multicenter Trial)

Objective: To assess the effectiveness, safety and cost-effectiveness of prophylactic NPWT in reducing the rate of SSIs after cesarean in obese women

Organization:

Study Sites – 1) Indiana University (IU Health Methodist Hospital & Eskenazi Hospital), Indianapolis Indiana; 2) Washington University in St. Louis School of Medicine; 3) University of Alabama at Birmingham; 4) Ochsner Medical Center, New Orleans 5) Mercy Hospital in St. Louis (Closed)

Study Coordinating Center: Indiana University Data Management Center: Washington University in St. Louis School of Medicine

Steering Committee – Tuuli (PI, chair), each of the site PIs, Caughey

Data Safety and Monitoring Board – Sindhu Srinivas, MD, MSCE(chair); Alison Cahill, MD, MSCI; Jenifer Allsworth, PhD

Design: Multicenter Randomized Clinical Trial

Inclusion criteria:

1. Pre-Pregnancy BMI ≥ 30 Kg/m^2 (BMI at first prenatal visit)
2. Gestational age ≥ 23 weeks
3. Scheduled/non-labor or unscheduled/labor cesarean delivery

Exclusion criteria:

1. Unwilling or unable to provide consent
2. Non-availability for postoperative follow-up
3. Contraindication to NPWT
   - Pre-existing infection around incision site
   - Bleeding disorder
   - Therapeutic anticoagulation
   - Allergy to any component of the dressing (e.g., silver, silicone, adhesive tape)
   - Prior irradiated skin

Allocation: Computer generated block randomization, stratified by study site, BMI category, scheduled/unscheduled cesarean

Sample size: **2850** (Standard dressing=1425, Prophylactic NPWT=1425)

Assumptions

1. Power=80% for primary outcome
2. Type 1 error=5% (2-sided)
3. Primary outcome
   -10% event rate with standard wound dressing
   -Anticipated 30% relative difference (anticipated 7% event rate with prophylactic NPWT)
4. 5% loss to follow up

Interventions:

1. Standard wound dressing
2. Prophylactic NPWT with Prevena™ (Peel & Place)

Management Protocols:

1. Prophylactic NPWT with Prevena™ (Peel & Place)
   - Place after skin closure
   - Remove on postop day #4, day of hospital discharge, or by day 7 if patient remains hospitalized
2. Standard wound dressing
   - Place after skin closure
   - Remove in approximately 24 - 48 hours

Outcome Measures:

Primary: Superficial or deep SSI within 30 days based on CDC criteria

Secondary:

- Individual components of the primary outcome (superficial or deep SSI)
- Organ space SSI (endometritis)
- Other individual wound complications: dehiscence ≥2 cm, hematoma, seroma
- Composite of any wound complications
- Pain and satisfaction scores at discharge, postoperative day 30
- Patient satisfaction with aesthetic appearance (scale of 0 - 10) at postoperative day 30
- Healthcare resource utilization: physician office or ED visits, antibiotics for SSI, hospital readmission for SSIs, home health for SSI, wound clinic for SSI
- Adverse events: skin blistering, allergic skin reactions, wound bleeding

Cost-effectiveness analysis

- Incremental cost per case of SSI prevented
- Incremental cost per Quality-adjusted Life-year (QALY).

Data Analysis:

Primary: Intention-to-treat

Secondary: Pre-specified subgroup, adjusted analyses, risk factors

Study Timetable:

Recruitment: 6 months to 54 months

Interim Analysis: @ N=1425 (50%) and N=2138 (75%)

1. Introduction

1.1. Abstract

The Prophylactic Negative Pressure Wound Therapy in Obese Women at Cesarean Trial is a large pragmatic multi-center randomized clinical trial designed to evaluate the effectiveness, safety and cost-effectiveness of prophylactic negative pressure wound therapy (NPWT) – a closed, sealed system that applies negative pressure to the wound surface via a single-use, battery-powered, portable device – to decrease surgical site infections (SSIs) in obese women. Experimental evidence suggests that NPWT promotes wound healing by removing exudate, approximating the wound edges, and reducing bacterial contamination. Obesity (body mass index [BMI] ≥30kg/m^2) increases the risk for both cesarean delivery and SSIs compared to non-obese women. The increased risk of SSIs is in part due to the increased thickness of the subcutaneous space, allowing collection of exudates and increasing tension on wound edges, promoting the growth of bacteria, and leading to wound infection and breakdown. Thus, prophylactic NPWT may be particularly effective in this patient population. During the 5-year project period, collaborating perinatal centers will randomize 2850 obese women undergoing cesarean delivery to receive either prophylactic negative pressure wound therapy with the Prevena^{TM} device or standard wound dressing. Women will be followed up to 30 days postoperatively to ascertain study outcomes. The primary outcome for the trial is superficial or deep SSI after cesarean according to the CDC National Healthcare Safety Network definitions. We will also assess other wound complications, adverse events potentially attributable to NPWT and incremental cost per case of SSI prevented and per quality-adjusted life year (QALY).

1.2. Specific Aims

Primary Aim: Determine the effectiveness of prophylactic NPWT in reducing the rate of SSIs after cesarean in obese women. *We hypothesize that obese women will have lower rates of SSIs after cesarean with use of prophylactic NPWT than with standard care.*

Secondary Aim#1: Assess the safety of prophylactic NPWT in obese women as measured by frequency of adverse events including skin blisters, allergic skin reactions, and wound bleeding. *We hypothesize that the rate of adverse events will not be significantly higher with use of prophylactic NPWT than with standard care.*

Secondary Aim#2: Evaluate the cost-effectiveness of prophylactic NPWT compared with standard wound dressing in obese women as measured by the incremental cost per case of SSI prevented and per quality-adjusted life year (QALY). *We hypothesize that prophylactic NPWT in obese women at cesarean will be cost-effective.*

1.3. Purpose of the Protocol

This protocol describes the background, design, and organization of the trial and represents a written agreement between study investigators. It will be reviewed and approved by the Data Safety and Monitoring Board (DSMB) and the Institutional Review Boards (IRBs) of each center prior to onset of recruitment. A **Manual of Operations** and **Data Collections Forms** will supplement this protocol with further details of study procedures.

2. Background

2.1. Introduction

SSIs are now the most common group of healthcare associated infections (HAIs) and are a significant cause of preventable morbidity and mortality in the United States.[1] These infections result in significant patient suffering and excess health care costs up to $10 billion each year.[1] For these reasons, prevention of HAIs is a top priority for the US Department of Health and Human Services and the Institute of Medicine.[2,3] Although several initiatives target HAIs, few are directed at SSIs after cesarean despite the fact that cesarean is the most common major surgical procedure performed in women. In 2013, 1.3 million cesareans were performed in the US and up to 12% of these were complicated by SSIs.[4,5] Puerperal infection is the 4th most common direct cause of maternal mortality in the US and one of the most common causes of morbidity.[6] Additionally, puerperal infection is an indirect or aggravating factor in many maternal deaths attributed to other causes. Moreover, cesarean delivery is the most important risk factor for puerperal infection.[2]

Obesity (BMI≥30 kg/m^2) further aggravates the problem of SSIs after cesarean: obese women are both more likely than non-obese women to deliver by cesarean[7-9] and are also at higher risk of SSIs.[10,11] Obesity complicates over 33% of pregnancies and morbid obesity (BMI ≥ 40 kg/m^2) complicates as many as 10% of pregnancies in the US. The trends of both increasing prevalence of obesity as well as increasing incidence of cesarean suggest that the burden of post-cesarean infections will continue to increase in the US.

2.1.1. Pathophysiology of SSIs after Cesarean in Obese Women

The mechanism for increased SSI risk in obese women is likely multifactorial. First, an excess of adipose tissue may result in dysregulation of the immune system, impairing chemotaxis and altering macrophage differentiation.[12] Obese women may also have diabetes and other metabolic derangements that further impair the immune system and thus the inflammatory phase of the wound healing process. Second, obesity decreases adipose tissue blood flow and alters collagen structure

and function,[13,14] limiting infiltration of the space by chemokines, macrophages and growth factors necessary for the first and second stages of wound healing. Obesity also impairs the penetration of preoperative antibiotics, resulting in tissue antibiotic levels below the minimal inhibitory concentration for pathogenic bacteria.[15] Third, the potential subcutaneous dead space allows accumulation of serous fluid and hematomas that serve as a nidus for infection.[16] Physiologic changes of pregnancy and intravenous fluids given during the puerperium exacerbate the accumulation of serous fluid in the subcutaneous dead space after cesarean. Fourth, the thickened subcutaneous tissue places additional mechanical stress on the wound, increasing both superficial stress and lateral tension. The additional shear stress reduces the apposition of cells in the incision, creating additional potential space and increasing the risk of wound dehiscence and infection. Finally, the overhanging pannus in obese women, especially over the site of Pfannenstiel incisions, creates a micro-environment conducive to bacterial proliferation.

2.1.2. Prophylactic Negative Pressure Wound Therapy

Negative pressure wound therapy (NPWT) is a closed, sealed system that applies negative (or sub-atmospheric) pressure to the wound surface. Used since the 1990s to treat open wounds, experimental evidence suggests that NPWT promotes wound healing by removing exudates, approximating the wound edges, and reducing bacterial contamination.[17-27] Two brands of a modified, single-use, battery-powered, portable NPWT devices Prevena™ (KCI USA, San Antonio, TX) and PICO™ (Smith & Nephew, Hull, UK) were recently FDA-cleared for prophylactic application after wound closure at the time of surgery. Although the precise mechanism of action of prophylactic NPWT is unclear, experimental evidence suggests that NPWT reduces bacterial contamination, edema, and exudates while increasing microvascular blood flow and promoting granulation tissue by inducing mechanical stress that promotes cell growth.[28-31] Computer and physical models of NPWT applied to closed incisions demonstrate a decrease in lateral tensile stress by 50% and in shear stress by more than 75%, leading to improved apposition of wound edges.[32] Given the proposed mechanisms of

increased SSI in obese women and the potential mechanism of action of prophylactic NPWT, we hypothesize that prophylactic NPWT will be particularly effective in this population.

2.1.3. Existing Data on Prophylactic NPWT

Non-Obstetric Patients

Prior studies of NPWT have largely been limited to cohort studies[33-37] and small randomized trials.[38-41] Whereas many demonstrated benefit in reducing SSIs and other wound complications, many studies were limited by small samples sizes and confounding by indication. A 2014 Cochrane review of seven randomized trials compared prophylactic NPWT to standard dressing among patients undergoing orthopedic and general surgical procedures. Data from only three of the trials could be combined in a meta-analysis, which showed no significant differences in the rate of SSI.[42] However, a fourth trial, in which data were analyzed by wound rather than by subject, showed a statistically significant 50% reduction in SSI in the NPWT group (14/144 (9.7%) versus 23/122 (18.9%), relative risk 0.52, 95% confidence interval 0.28-0.96). The authors concluded that "there is an urgent need for suitably powered, high-quality trials to evaluate the effects of the newer NPWT products that are designed for use on clean, closed surgical incisions." No studies of prophylactic NPWT after cesarean were included in this review.

Obstetric Patients

We identified three retrospective cohort studies and one pilot randomized trial in a systematic review of studies on prophylactic NPWT in obese women after cesarean[43-46]: (**Table 1**). Two of the retrospective cohort studies compared obese women who received prophylactic NPWT after cesarean to historical controls who received standard dressing. Both studies demonstrated a dramatic reduction in SSIs, reporting no SSIs in the intervention group but 10.4% and 12.0% in the standard dressing controls.[43,44] The third retrospective study included women who had labored prior to cesarean with at least one additional risk factor for SSI (obesity, preeclampsia, and chorioamnionitis). In this study

prophylactic NPWT was associated with a statistically significant reduction in the risk of wound infection (2.7% versus 11.5%; RR 0.24, 95% 0.07, 0.77; P=0.006) and endometritis (0.9% vs 6.7%, p=0.023).[46]

Table 1: Published studies on use of prophylactic NPWT at cesarean in obese women

Study	Design	Device	Inclusion	Surgical site infections, n/N (%)		Relative Risk (95%CI)	Limitations
				NPWT	Control		
Mark et al.,2013	Retrospective cohort	Prevena	BMI>45	0/21 (0%)	5/48 (10.4%)	0.20 (0.01, 3.50)	Small sample size, possible selection bias and confounding by indication
Bullough et al.,2014	Retrospective cohort	PICO	BMI>35	0/50 (0%)	6/50 (12%)	0.08 (0.00, 1.33)	Small sample size, possible selection bias and confounding by indication
Swift et al.,2015	Retrospective cohort study	Prevena	BMI>30 or other risk factors	3/110 (2.7%)	24/209 (11.5%)	0.24 (0.07, 0.77)	Non-randomized design, possible confounding, modest sample size
Chaboyer et al.,2015	Pilot Randomized Controlled Trial	PICO	BMI>30	10/44 (22.7%)	12/43 (27.9%)	0.81 (0.39, 1.68)	Small sample size, included only elective cesareans, possible confounding

Chaboyer et al recently published a pilot randomized trial in which 87 obese women undergoing elective cesarean were randomized to prophylactic NPWT or standard dressing.[45] Use of prophylactic NPWT was associated with a statistically non-significant 19% decrease in SSI (22.7% vs 27.9%; RR 0.81, 95% CI 0.38-1.68). The authors also found no differences in the frequencies of adverse events (7/44 [15.9%] with NPWT vs 7/43 [16.3%] with standard dressing), and all were minor (skin blisters, erythema, bruising, and wound bleeding). Although more methodologically sound than the others, this

study was limited by including only elective cesareans, the small sample size and differences in prognostic baseline characteristics between the two groups.

Taken together, these studies suggest a 65% decrease in SSIs after cesarean with prophylactic NPWT (random effects model: pooled RR 0.35, 95% CI 0.12-1.04). Although results of these studies are promising, the small sample sizes, between-study heterogeneity, and methodological limitations preclude definitive conclusions on the effectiveness of prophylactic NPWT in obese women after cesarean.

Preliminary Study#1

We conducted a retrospective cohort study at one of the proposed study sites (University of Alabama at Birmingham) where some physicians use the NPWT in select morbidly obese women undergoing cesarean. The charts of all women with a BMI ≥40 kg/m^2 undergoing cesarean since NPWT became available were reviewed. Of 762 subjects, 15 received NPWT. Women who received NPWT weighed more (BMI 68.8 versus 50.0, *P*<0.01) and were more likely to have medical co-morbidities than those who did not receive NPWT. The risk of SSI was remarkably lower with prophylactic NPWT (0% [0/15] versus 11.9% [89/747], *P*=0.16) (**Fig.1**). Although the study is limited by the non-randomized design, small sample size, and selection bias, the results suggest that prophylactic NPWT may be effective in reducing SSIs after cesarean in obese women.

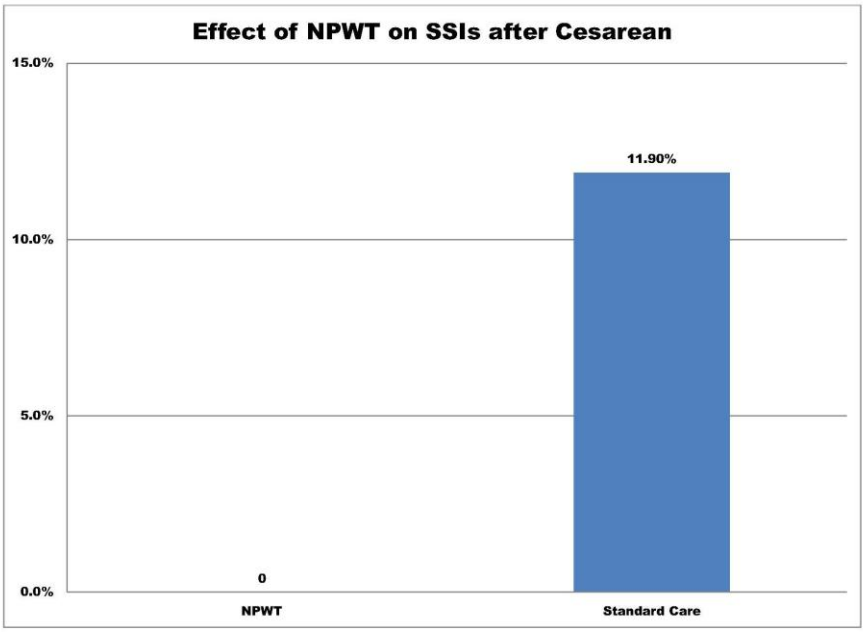


Figure 1: Effect of NPWT on SSIs after Cesarean

Preliminary Study#2

We conducted a pilot RCT (planned N=120) at Washington University Medical Center[47] aimed at: i) assessing the willingness of obese patients to participate in an RCT of prophylactic NPWT after

cesarean, and ii) testing the logistics needed for the trial. We obtained IRB approval for the trial and developed a study protocol. Obese women in labor completed a survey and 67% stated willingness to participate in the study. We consented and randomized 120 obese patients undergoing cesarean in 6 months.

2.2. Adverse Effects of Prophylactic NPWT

The Single Use Prophylactic Negative Pressure Wound Therapy System received FDA marketing approval in 2012. As of September 2015, we identified two reports on the FDA website of blistering at the site of application from the PICO device. A third report of a minor burn from the PICO pump device occurred in a patient after neurosurgery while still unconscious. The patient was found to have been lying on the pump device for a prolonged period of time.

A high rate of skin blisters was reported when NPWT was used after orthopedic surgery, but not with other surgical procedures. This was attributed to use of the adhesive dressing in the setting of marked swelling and edema[48]. Case series suggest approximately 10-15% rate of skin irritation and blisters at the device application site. The majority (~90%) did not require treatment beyond removal of the device.[49,50] Moreover, adverse events noted with NPWT after cesarean were minor and comparable in frequency to standard dressing[51].

2.3. Cost-benefit of Prophylactic NPWT

The current FDA-cleared prophylactic single-use NPWT devices cost between $200 (PICO™) and $500 (Prevena™) per unit and are increasingly being used after cesarean. Given the cost, prophylactic NPWT must be shown in an independent, suitably powered, high-quality trial to improve clinical outcomes to justify widespread use[52]. However, if proven to be effective at reducing SSIs after cesarean, use of the device may not only be cost-effective, but cost-saving. Two cost-effectiveness analyses of prophylactic NPWT have recently been published suggesting that use prophylactic NPWT after cesarean may be cost effective under a range of conditions. However, because data on its

effectiveness at cesarean are lacking, the cost-effectiveness analyses were based on data extrapolated from other surgical procedures[49,53]. In addition to the effectiveness data this trial will produce, the accompanying cost-effectiveness analysis will aid decision-making on general clinical use[52].

2.4. Rationale for the Trial

Infection is one of the top five causes of pregnancy-related death and morbidity in the US and around the world. As rates of cesarean - the strongest risk factor for puerperal infection - continue to rise, the burden of infection is anticipated to increase. Obese women are at particularly high risk of infection after cesarean. Despite the dramatically increased risk of SSI in obese women, no specific intervention exists in this population. Preliminary data from published retrospective cohorts and small randomized trials, as well as our pilot data suggest that prophylactic NPWT may decrease SSI in obese women undergoing cesarean. Therefore, given 1) the persistent high risk of infection and attendant individual and public health costs among obese women undergoing cesarean, 2) the increasing trend in both cesarean and obesity, 3) preliminary data suggesting the effectiveness of NPWT for preventing SSI, and 4) increasing use of NPWT devices with healthcare cost implications, a multicenter trial evaluating the effectiveness, safety and cost-effectiveness of prophylactic NPWT after cesarean in obese women is important and timely.

3. Study Design

3.1. Research Questions

Primary Question

Compared to standard wound dressing, does the use of prophylactic NPWT reduce the risk of surgical site infection after cesarean in obese women?

Hypothesis: Compared to standard wound dressing, prophylactic NPWT reduces the incidence of post-cesarean surgical site infection in obese women.

Secondary Question 1

Is the use of prophylactic NPWT associated with increased adverse events such as skin blisters, allergic reaction, wound bleeding?

Hypothesis: Compared to standard wound care, prophylactic NPWT will not be associated with a significantly higher incidence of adverse events.

Secondary Question 2

Is the use of prophylactic NPWT after cesarean in obese women cost-effective?

Hypothesis: Prophylactic NPWT will be a cost-effective intervention for the prevention of surgical site infections after cesarean in obese women.

3.2. Design and Rationale

This is a pragmatic multicenter randomized controlled trial. We chose a randomized controlled trial, the 'gold standard' of clinical research design, with the goal of obtaining the highest quality evidence to inform clinical practice. The broad inclusion criteria and evaluation of effects of typical use of prophylactic NPWT make this a pragmatic trial. The multicenter design and inclusion of both academic and community hospitals in two regions of the U.S. with high rates of obesity increase generalizability and direct application of the findings[54]. We will follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines in the conduct and reporting of this trial[55]. Analysis will follow the intention-to-treat principle. By random allocation, patients will receive either prophylactic NPWT or

standard wound care after cesarean delivery. The remainder of perioperative care will be similar for both arms including the administration of standard preoperative antibiotics within 60 minutes prior to skin incision, skin preparation with chlorhexidine alcohol or povidone-iodine solution, and clipping (rather than shaving) of hair as needed prior to incision.

3.3. Eligibility Criteria

3.3.1. Inclusion Criteria

- Gestational age ≥23 weeks
- Pre-pregnancy BMI ≥ 30 Kg/m^2 (based on BMI at first prenatal visit, but BMI at delivery will also be collected)
- Undergoing scheduled or unscheduled cesarean delivery

3.3.2. Exclusion Criteria

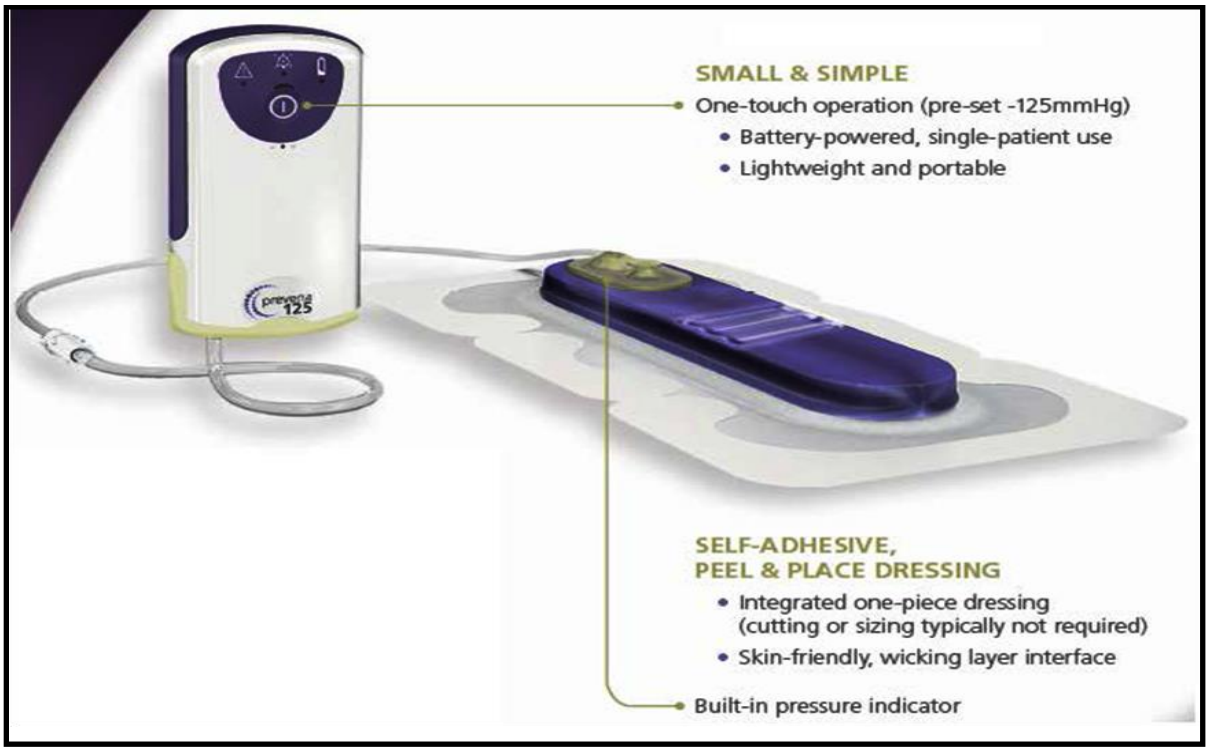
- Patient unwilling or unable to provide consent
- Non-availability for postoperative follow up
- Contraindication to NPWT applicable to women undergoing cesarean
    - Pre-existing infection around incision site
    - Bleeding disorder
    - Therapeutic anticoagulation
    - Allergy to any component of the dressing including silver, silicone and adhesive tape
    - Prior irradiated skin

4. Study Procedures

4.1. The Prevena™ Incision Management System (Peel & Place)

The Prevena™ Incision Management System incorporates all of the functional elements of NPWT that are necessary for management of closed surgical incisions. The system has the added advantages of being simple in concept and having an anatomically adaptable peel-and-place dressing which is uniquely designed to be skin-friendly. The dressing is easy to apply and use in the operating room (OR) by the surgeon, study staff or surgical staff. The system may also transition from the OR to the hospital and/or outpatient setting for use by multiple care takers.

Figure 1: The Prevena™ Incision Management System (Peel & Place)



The Prevena Incision Management System consists of the following components:

- The Prevena™/ Prevena PLUS™ Incision Management System that is applied over clean sutured or stapled incisions in a simple peel-and-place process and applies continuous negative pressure at 125 mmHg through the dressing to the incision site. The Prevena™

Incision Management System accommodates incisions up to 20 cm in length and the Prevena PLUS™ Incision Management System accommodates incisions up to 35 cm in length.

- The dressing has a built-in pressure indicator that when compressed indicates that the negative pressure in the system is between -75mmHg to -125mmHg. A raised pressure indicator button indicates that the negative pressure is less than 75mmHg.
- A polyurethane coated, polyester fabric interface layer with 0.019% ionic silver wicks fluid from the skin surface. The silver is not intended to treat infection but only to reduce bacterial colonization within the fabric.
- The polyurethane foam bolster that covers the interface layer has a pore size of 400-600 microns and a violet colorant; the foam manifolds negative pressure to the incision site.
- A polyurethane film with acrylic adhesive provides adhesion of the dressing to the skin surrounding the incision. A polyurethane shell encapsulates the foam bolster and interface layer, providing a closed system.
- The unit is battery powered for seven days, lightweight, easily portable and designed for single patient use.
- The Prevena™ 45mL canister or the Prevena PLUS™ 150mL canister for collection of incision exudate.
- Prevena Patch Strips, which may be used to help seal leaks around the dressing
- All patient-contact materials are free of latex and DEHP [Di (2ethylhexl) phthalate].

4.2. Provider Training on Use of NPWT Device

All research staff and clinicians (labor & delivery and postpartum nurses, OR technicians, physicians) involved in the study will receive formal training on how to place and remove the prophylactic NPWT device.

- Providers will have to demonstrate proficiency and receive certification by a KCI Representative in order to be part of the study

- Content of the training
    - Placement of the dressing over the wound
        - The dressing will be placed centrally over the wound to reduce the chance of wound fluid coming into contact with the port
        - Placement of the dressing so that the port should be uppermost from the wound and placed over intact skin
        - The dressing should be applied so that the border of the dressing is not creased.
        - Insertion of batteries into the pump
        - Connecting the pump to the dressing by twisting together the tubing connectors
        - Application of fixation strips around 4 sides of the dressing
        - Activation of the device to initiate negative pressure
        - Troubleshooting if negative pressure is not achieved
        - Inspection of dressing and indications for dressing change
    - Patients instructions on pump use
        - Disconnection of the pump for showering
        - Not to submerge dressing in water
        - Wiping the pump clean with a damp cloth using soapy water
        - When to notify the nurse or physician: all pump lights are off (pump is off), if amber light is flashing (indicating a leak), or if all lights are illuminated (indicating a pump failure)

4.3. Screening

Study personnel at each clinical site will screen and consent patients under the direction of the site PI. Patients will be enrolled at the time of admission for delivery or anytime thereafter prior to cesarean. Each center will have the flexibility to use an approach that is most efficient and suitable for their system to screen and consent patients. Medical records of all potential patients admitted for

delivery will be reviewed and those who satisfy inclusion and exclusion criteria will be approached and written informed consent obtained. A screening log will be used to track all patients approached for the study.

4.4. Randomization

Women will only be randomized once the decision is made to do a cesarean. A confidential web-based randomization sequence will be prepared by using blocks of variable sizes, stratified by study site, BMI category (30-39.9 and ≥40 kg/m^2) and scheduled/non-labor versus unscheduled/labor cesareans. The randomization sequence will be maintained centrally by the study statistician. The patient's group assignment will be revealed once basic information including confirmation of the inclusion criteria are submitted online.

4.5. Procedures

Schedule of Events

	Enrollment	PP Day 2-7 or Day of Discharge	1-2 weeks Postpartum	Post-Op Day 30 (+/- 2 days)	4-6 weeks Postpartum
Eligibility and Randomization	X				
Interview: Maternal Demographic Characteristics	X				
Skin Swabs/Adipose Tissue Biopsies	X				
Chart abstraction: Prenatal Records		X			
Chart abstraction: Fetal/Neonatal outcomes		X			
Patient Satisfaction Survey		X			
AE/SAE Form		X	X	X	X
Chart abstraction: Outcome Assessment		X	X	X	X
Phone Call/Follow Up Survey		X		X	
Chart abstraction: Post Partum Form					X

Preoperative care

Routine preoperative cesarean care at each center will be given to patients by their clinical providers. These procedures are similar and all study sites have agreed on basic standardization of SSIs prevention strategies as well as diagnosis and treatment (**Table 2**).

Standardized preoperative procedures include:

- Clipping of hair at site of incision immediately prior cesarean as needed
- Preoperative antibiotics within 60 minutes prior to incision. Typical preoperative antibiotic used is 2-3 g of cefazolin. Penicillin-allergic patients will receive gentamicin and clindamycin. Patients with chorioamnionitis will receive ampicillin, gentamicin, and clindamycin.
- Skin preparation with chlorhexidine-alcohol or povidone-iodine solution with 3-minutes of drying time prior to draping.
- Adherence to these procedures will be recorded and monitored.

Intraoperative care

- Choice of incision will be left to the surgeon. The typical incision for a cesarean is a Pfannenstiel (low transverse) skin incision, although body habitus (particularly in obese women) and prior surgeries may dictate the use of a high transverse skin incision above the pannus or a vertical midline skin incision
- The preferred uterine incision will be low transverse, unless intraoperative findings such as dense adhesions or poorly developed lower uterine segment necessitate a classical or high transverse incision
- Closure of the subcutaneous layer if ≥2 cm
- The preferred skin closure at the participating centers is subcuticular suture. However, type of incision, scar tissue, and patient preference may play a role in the decision to use staples

Table 2: Routine infection prevention practices at each study site

	Washington University in St. Louis	**University of Alabama at Birmingham**	**Ochsner Medical Center**	**Mercy Hospital in St. Louis**	**Indiana University**
Hair clipping	Clipping immediate preop if needed	Clipping immediate preop if needed	Clipping immediate preop if needed	Clipping immediate preop if needed	Clipping immediate preop if needed
Skin Prep	Chlorhexidine-alcohol; iodine-alcohol if allergic to chlorhexidine	Povidone-Iodine + Chlorhexidine-alcohol; chlorhexidine gluconate alone for urgent cases	Chlorhexidine for non-urgent cases; betadine for urgent	Betadine-alcohol, chlorhexidine-alcohol for betadine allergy	Chlorhexidine-alcohol for non-urgent cases; betadine for urgent
Antibiotics	Administer Preoperatively Cefazolin: 2g if >80kg, 3 g for >160 kg. If laboring Azithromycin is added. If cephalosporin allergy: gentamicin 2 mg/kg + 900 mg clindamycin.	Administer Preoperatively Cefazolin: 2g if >80kg, 3 g for >160 kg. If laboring Azithromycin is added. If cephalosporin allergy: gentamicin 2 mg/kg + 900 mg clindamycin	Administer Preoperatively Cefazolin: 2g if >80kg, 3 g for >160 kg. If laboring Azithromycin is added. If cephalosporin allergy: gentamicin 2 mg/kg + 900 mg clindamycin	Administer Preoperatively Cefazolin: 2g if >80kg, 3 g for >160 kg. If laboring Azithromycin is added. If cephalosporin allergy: gentamicin 2 mg/kg + 900 mg clindamycin	Administer Preoperatively Cefazolin: 2g if >80kg, 3 g for >160 kg. If laboring Azithromycin is added. If cephalosporin allergy: gentamicin 2 mg/kg + 900 mg clindamycin
Delivery of placenta	Spontaneous	Spontaneous	Manual	Spontaneous	Spontaneous
Subcutaneous layer	Closure if >2cm	Closure if >2cm	Closure if >2cm	Closure if >2cm	Closure if >2cm
Skin closure	Subcuticular suture	Subcuticular suture	Most subcuticular suture; rare staples	Most subcuticular suture; rare staples	Most subcuticular suture; rare staples

Standard wound dressing	Honeycomb dressing stays in place for 24 hours	Honeycomb dressing stays in place for 48 hours	Abdominal pressure dressing x24 hours	Abdominal pressure dressing x24 hours	Abdominal pressure dressing x 24 hours

- As this is a large pragmatic trial, and many factors play a role in operative decisions, the operative procedures used will be recorded and the impact of these variations on the effectiveness of prophylactic NPWT will be assessed in secondary analyses.

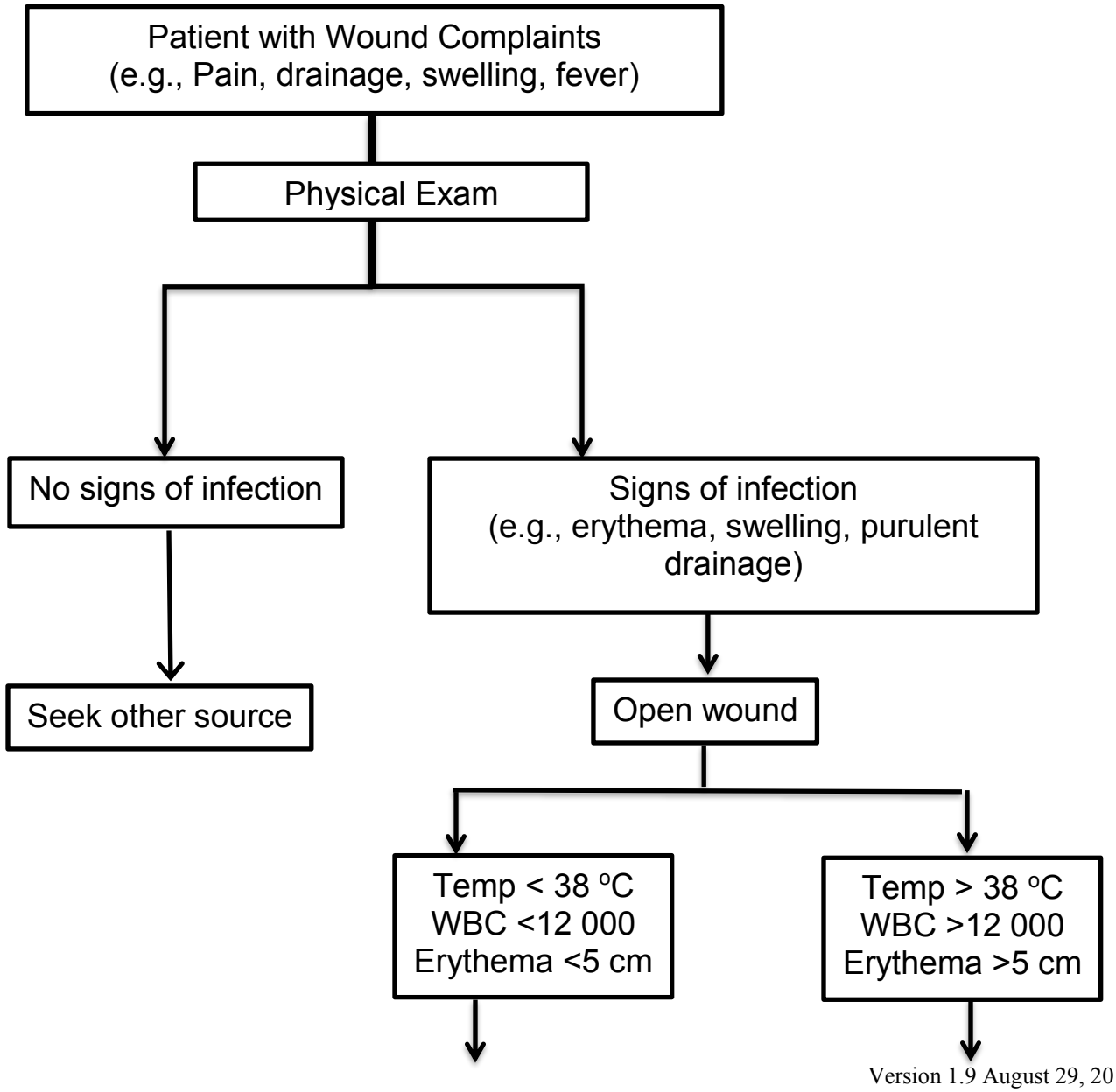
Postoperative care

- Patients will be monitored daily while in the hospital
- Removal of standard surgical dressing at approximately 24 hours in patients randomized to standard dressing
- We will plan to remove the negative pressure wound therapy dressing on postoperative day #4 or day of discharge in patients randomized to prophylactic NPWT with Prevena™ /Prevena PLUS™. However, patients who remain hospitalized will have the device on for up to 7 days. Therefore, the minimum duration of therapy will be 2-4 days with an anticipated average of duration of approximately 5 days.
- Replacement of any dressing that is saturated
- If a patient develops infection with the NPWT device in place the device will be removed and the patient given standard SSI therapy as outlined below
- Patients will be educated about the signs and symptoms of infection and other study outcomes and encouraged to call their provider
- Research staff will monitor subjects' inpatient course for signs and symptoms of SSI
- Management of surgical site infections will follow the Practice Guidelines of the Infectious Diseases Society of America[56]
- All patients will sign a medical record release which will be faxed to any hospitals or physician's office to obtain records for review

- All clinical sites will follow policies to routinely send specimens for culture and sensitivity from all accessible infections such as wound/skin infections or drained abscesses in order to identify individual infectious agents and their antibiotic susceptibilities. Outcomes pertaining to microbial resistance will be obtained through subject chart abstraction.

  The following infant data will be collected after delivery: Gender, weight, well baby, special care nursery or NICU, APGAR scores, umbilical cord blood gas results, neonatal outcomes and any complications will be collected.

Figure 2: Algorithm for the management and treatment of surgical site infections (SSIs)[56]



*Choice of antibiotics will be based on infection severity and local bacteria resistance patterns by the subject's clinical care provider.

4.6. Follow Up

- We will use active surveillance by research staff to ascertain surgical site infections.
- Research staff will follow-up with the research participant on the day of discharge or within 48 hours (postpartum day 2-7) to assess for adverse events, assess the participant's pain and obtain their satisfaction with their dressing.
- Research staff will call subjects on approximately postoperative day 30 (±2 days). They will ask the patient standardized questions regarding wound complications. If the patient reports a hospital, clinic, or ER visit not associated with the study centers, the staff will obtain the name of the medical facility and request the records.
- The EQ-5D-3L quality of life questionnaire will be administered at the 30-day call.
- Typically, patients will have routine follow-up with their provider scheduled at 1-2 weeks and 4-6 weeks post-partum.
- We will obtain medical records from each of those clinic visits as well as records of unscheduled visits (to any hospital clinic or ER) to ascertain study outcomes

4.7. Withdrawals

Patients who withdraw from the study after randomization will be excluded from further follow-up. However outcomes ascertained up until the time of withdrawal will be reported in the intent-to-treat analysis.

4.8. Outcome Measures

4.8.1 Primary Outcome

Superficial or deep surgical site infections as defined according to the CDC's National Healthcare Safety Network criteria. Diagnosis will be made by the treating physician and reviewed and validated centrally by the PI against the *CDC's National Healthcare Safety Network Definitions of Surgical Site Infections* and blinded to intervention group

A **superficial incisional (or wound) SSI** must meet the following criteria: Infection occurs within 30 days after the operative procedure AND involves only skin and subcutaneous tissue of the incision AND patient has at least one of the following: i) purulent drainage from the superficial incision; ii) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision; iii) at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon, and is culture-positive or not cultured (a culture-negative finding does not meet this criterion); iv) diagnosis of superficial incisional SSI by the surgeon or attending physician.

A **deep incisional (or wound) SSI** must meet the following criteria: Infection occurs within 30 days after the operative procedure AND involves deep soft tissues (e.g., fascial and muscle layers) of the incision AND patient has at least one of the following: i) purulent drainage from the deep incision but not from the organ/space component of the surgical site; ii) a deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive or not cultured when the patient has at least one of the following signs or symptoms: fever (>38°C), or localized pain or tenderness (a culture-negative finding does not meet this criterion); iii) an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination; iv) diagnosis of a deep incisional SSI by a surgeon or attending physician.

4.8.2. Secondary Outcomes

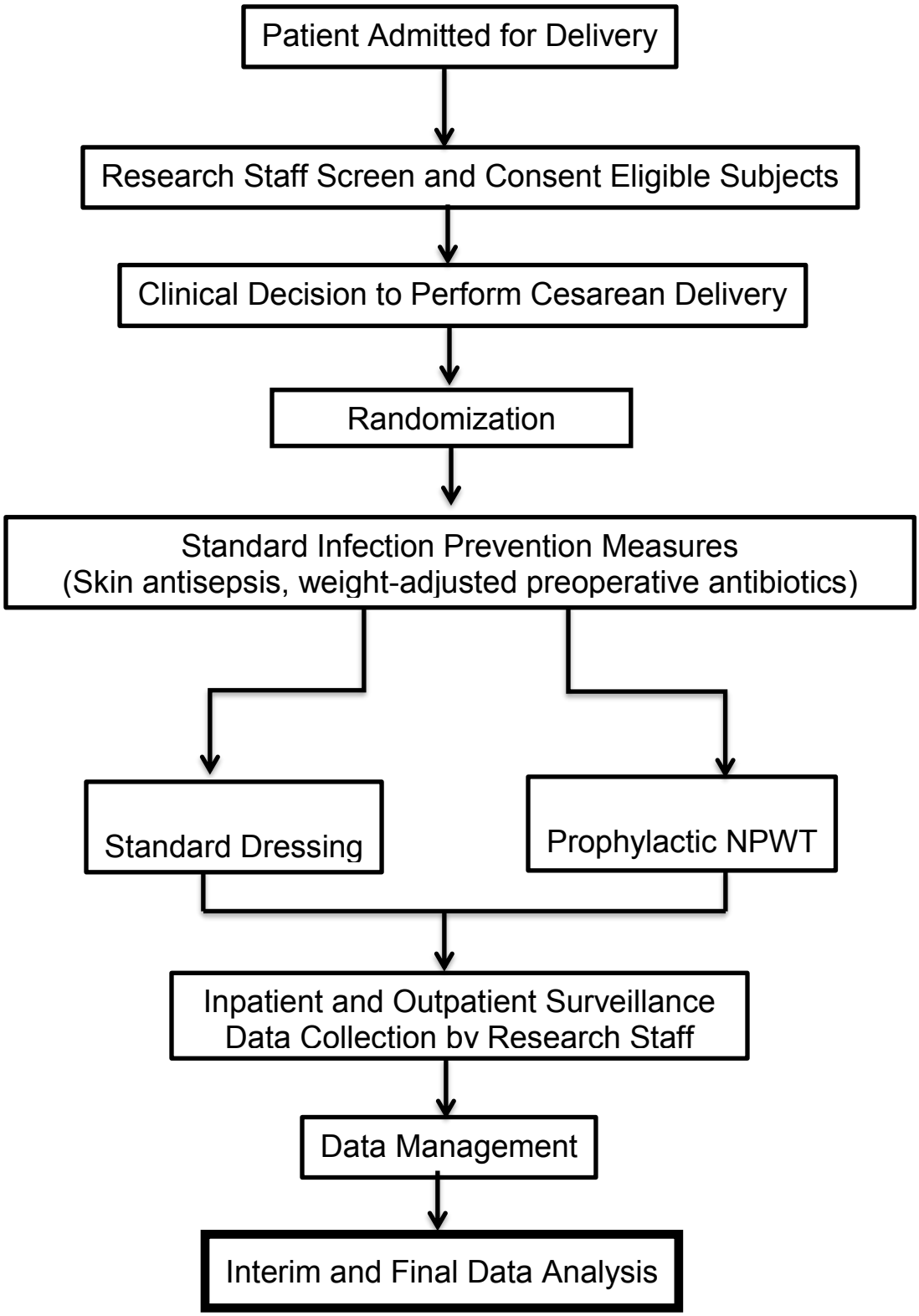
- Individual components of the primary outcome (superficial or deep SSI)
- Organ space SSI (endometritis)
- Other individual wound complications: dehiscence ≥2 cm, hematoma, seroma, erythema

- Composite of any wound complications
- Patient pain and satisfaction scores at discharge and postoperative day 30
- Patient satisfaction with aesthetic appearance (scale of 0 - 10) at postoperative day 30
- Healthcare resource utilization: physician office or ED visits, antibiotics for SSI, hospital readmission for SSIs, home health for SSI, wound clinic for SSI
- Adverse events: skin blistering, allergic reaction, wound bleeding

4.8.3. Cost-effectiveness analysis outcomes

- Incremental cost per SSI prevented
- Incremental cost per QALY

Figure 3: Summary of Study Flow and Procedures



5. Data Management

5.1. Data Collection

We will collect detailed antepartum, intrapartum, and postpartum information from study participants into a comprehensive database.

- Trained research staff in obstetric and perinatal outcomes abstraction at each center will be responsible for all research data abstraction from patient records
- Research staff will undergo centralized specific training to ascertain study outcomes
- Standardized information will be abstracted from all charts regardless of study group
- Relevant data will be collected initially to assess eligibility. Complete baseline, outcome, wound culture, and cost data will be collected via direct interview and chart review
- Several data collection forms will be used during these processes, including forms for maternal baseline data, preoperative and intraoperative care, maternal outcomes, postpartum clinic/hospital outcomes, and Quality of Life Questionnaire (EQ-5D-3L)
- Data on these forms devoid of personal identifiers will be securely sent to the data management center through web-based entry

5.2. Specimen collection and storage for future studies

- Subjects will be asked to participate in an optional biospecimen collection in which their samples will be stored for batched analysis. These samples may be used for future research studies or shared with other researchers. These samples may include:
    - Skin swabs at the incision site before skin prep
    - Skin swabs at the incision site after skin prep
    - Subcutaneous adipose tissue biopsy prior to fascial incision
    - Subcutaneous adipose tissue biopsy after fascial closure
- All specimens will be processed per the Manual of Operations and stored at -80 degrees Celsius +/-2 degrees until analysis

5.3. Data Processing

The Data Management Center (DMC) at Washington University School of Medicine will be responsible for data management and analysis in accordance with the analysis plan to be finalized by the steering committee and approved by the DSMB. The Data Management Team based at Washington University includes an experienced statistician and a database manager. Each site PI and nurse coordinator will be responsible for liaison with the DMC including transmitting de-identified abstracted information contained in the data collection forms. Data management at each site will include: procedures for data entry, data editing, and compilation; procedures for data transmittal; and procedures for quality control, data verification, confidentiality and security. Data will be collected and managed with REDCap (Research Electronic Data Capture), an established, secure, web-based data capture and management tool developed at Vanderbilt University and supported by the bioinformatics team at WUSM (http://www.biostat.wustl.edu/redcap/). The security of the database will be maintained by the use of dedicated password protected encrypted computers with multiple private backups (daily, weekly, and monthly including on- and off-site storage for protection against disaster).

5.4. Loss to follow-up and missing data

We will employ strategies we have used in prior studies to achieve excellent follow-up and minimal missing data. Because patients will require necessary postoperative and postpartum visits, there will be ample opportunity for follow-up. In addition, we will obtain two contact numbers from subjects when available and contact them on approximately postoperative day 30 (±2 days). We will also obtain written authorization to obtain records from their Emergency Room and physician office visits and hospital readmissions. We will employ active data management at each site, including monthly data review for rates and patterns of missing data. Remedial measures including re-abstraction of data and retraining of staff will be used as needed to minimize missing data. If data are still missing, we will address the deficiency analytically[57]. We will first determine if data is missing at

random. We will then employ methods including multiple imputations and sensitivity analyses to test the robustness of our results.

6. Data Analysis

6.1. Sample Size and Power

6.1.1. Primary Aim – Effectiveness

The total sample size for the trial is estimated based on the primary outcome. We then estimate, on the basis of the sample size for the primary aim, the power we will have to detect clinically significant differences in the secondary aims. All sample size and power estimates are based on two-tailed tests, enabling us to detect an increase or decrease in rates of outcomes with use of prophylactic NPWT.

The baseline rate of SSIs in obese women from our preliminary data is 11.6%. Furthermore, rates of SSIs at the study sites in all women range from 6 to 12% and are expected to be higher in obese women. Assuming a conservative baseline rate of 10%, we estimate that a total of **2850** subjects (1425 NPWT and 1425 standard care) will be sufficient to detect a 30% relative difference in SSIs, with 80% power and 5% significance level and accommodation of 5% loss to follow-up (**Table 4**). This 30% difference represents the difference between a 10% rate of SSI in the standard care group and a 7% rate in the NPWT group.

Table 4: Sample size estimation
(Power=80%, 2-tailed, α =0.05)

Detectable relative difference	Anticipated SSI rate with NPWT (assuming 10% baseline rate)	Sample size (assuming 5% loss to follow-up)
50%	5.0%	910
40%	6.0%	1514
33%	6.7%	2316
30%	**7.0%**	**2850**
25%	7.5%	4215
20%	8.0%	6760

6.1.2. Secondary Aim 1 - Safety

The sample size of 2,850 subjects for the primary aim will be sufficient to detect at least a 25% difference in composite adverse events between the two groups with 85% power and significance

level of 5%. This represents the difference between a 16% rate of composite adverse events with NPWT (based on preliminary data[58]) and 12% with standard dressing.

6.1.3. Secondary Aim 2 – Cost Effectiveness

A recent cost-effectiveness analysis estimated a 400 to 600 patients as the adequate sample size of a future trial investigating cost- effectiveness of prophylactic NPWT at cesarean[53]. Thus, our sample size of 2850 for the primary outcome will provide sufficient power for the cost-effectiveness analysis.

6.2. Data Analysis Plan

6.2.1. Primary Analyses

Data analyses will adhere closely to the CONSORT guidelines[55]. Analyses will follow the intention-to-treat principle in which subjects will be analyzed in the group to which they were randomized, regardless of whether or not they received the assigned intervention.

Descriptive statistics will characterize the group of individuals recruited and investigate comparability of the two groups at baseline. Formal statistical testing will be limited to selected baseline characteristics considered to be prognostic factors for the primary outcome such as emergent cesarean, type of skin incision, and prolonged rupture of membranes. The categorical prognostic factors will be compared between trial groups by using the Chi-squared or Fisher's exact tests as appropriate. The two-group independent t-test and Mann-Whitney U test will be used to compare normal and non-normally distributed continuous variables, respectively. The primary outcome and other categorical secondary outcomes will be compared between intervention groups by using the Cochran-Mantel-Haenszel test. We will calculate common relative risks and 95% confidence intervals associated with the primary and secondary outcomes.

We will use the Breslow-Day test to assess homogeneity of the effect across subgroups (study sites, BMI category [30 – 39.9, ≥40], and scheduled/non-labor or unscheduled/labor cesareans, skin incision type [low transverse, high transverse, midline vertical], diabetes status). We will also conduct time-to-event analyses by using Kaplan Meier and Cox regression models to examine the pattern of SSIs in the two groups.

6.2.2. Secondary Analyses

Adjusted estimates

We will perform analyses aimed at obtaining estimates of treatment effectiveness, adjusting for any imbalances in baseline subject characteristics between groups. The objectives of these analyses are to estimate the influence of covariates on the outcome and to use them to improve the estimated difference between treatment groups. Logistic regression models will be used to identify and estimate the effect of multiple prognostic factors on the probability of SSI and other categorical outcomes.

Cost-Effectiveness Analysis

The economic analysis will be led by Aaron Caughey, MD, MPP, MPH, PhD, an MFM Specialist and Health Economist with extensive experience in cost-effectiveness analysis. We will adhere closely to the guidelines for economic analysis accompanying clinical trials set forth by the international Task Force on Good Research Practices on RCT Cost-Effectiveness Analysis[59,60]. The primary perspective of this economic evaluation will be societal, but we will also examine the patient and health care payer perspectives. This analysis will follow the intention-to-treat principle. The time horizon for the analysis will be the 30-day follow-up period of the trial, but we will include costs for treatment of SSIs beyond 30 days. Costs and effects will not be discounted because the time horizon for the analysis is short.

Costs: Direct medical costs will be the primary measure, but indirect costs may be considered if feasible. Direct medical costs will include the cost of implementing prophylactic NPWT or standard dressing (e.g., device or dressing cost, treatment of side effects), and medical care for SSI (e.g., hospital costs, emergency room, outpatient services, wound care supplies, and medications). Indirect costs will include cost of traveling for outpatient visits and lost productivity from being absent from work or usual activity. Secondary data sources will be used as much as possible to reduce the burden of data collection for economic analysis. Unit costs for inpatient and outpatient services, outpatient procedures, laboratory tests, and office visits will be estimated by using charges adjusted for cost-to-charge ratios. The unit cost of medications will be derived from average wholesale prices. Unit costs for study patients' time will be based on the average national wage rate.

Effectiveness: The effectiveness measures will be rate of SSI and QALYs. We will calculate QALYs by applying utility weights (1=perfect health, 0=death) to various health states values derived from the EuroQol five dimensions questionnaire **(EQ-5D).** The EQ-5D is a standardized instrument for measuring generic health status. The health status measured with EQ-5D-3L is used for estimating preference weight for that health status, then by combining the weight with time, QALYs can be computed. We will administer the EQ-5D to patients at the 30-day follow-up phone call. Once the data have been collected a scoring function can be used to assign a value (i.e., EQ-5D™ index score) to self-reported health states from a set of U.S.-generated value set (preference weights)[61].

EQ-5D is one of the most commonly used generic health status measurement, and its good validity and reliability have been reported in various health conditions. The EQ-5D-3L questionnaire is made up for two components; health state description and evaluation. In the description part, health status is measured in terms of five dimensions (5D); *mobility, self-care, usual activities, pain/discomfort, and anxiety/depression*. Mobility dimension asks about the person's walking ability. Self-care dimension asks about the ability to wash or dress by oneself, and usual activities dimension measures performance in "work, study, housework, family or leisure activities". In the pain/discomfort

dimension, it asks how much pain or discomfort they have, and in the anxiety/depression dimension, it asks how anxious or depressed they are. The respondents self-rate their level of severity for each dimension using a three-level (3L) scale: *having no problems, having some or moderate problems, being unable to do/having extreme problems*. In the evaluation part, the respondents evaluate their overall health status using the visual analogue scale (EQ-VAS) which ranges from 0 (the worst health you can imagine) to 100 (the best imaginable health state).

Cost-effectiveness: The measures of cost-effectiveness of prophylactic NPWT will be incremental cost per case of SSI prevented and incremental cost per QALY. They will be calculated as follows.

Incremental cost per case of SSI prevented:

$$(\text{Mean Cost}_{\text{Prophylactic NPWT}} - \text{Mean Cost}_{\text{standard care}}) \div (\text{Mean SSI Rate}_{\text{Prophylactic NPWT}} - \text{Mean SSI Rate}_{\text{standard care}})$$

Incremental cost per QALY:

$$(\text{Mean Cost}_{\text{Prophylactic NPWT}} - \text{Mean Cost}_{\text{standard care}}) \div (\text{Mean QALY}_{\text{Prophylactic NPWT}} - \text{Mean QALY}_{\text{standard care}})$$

All estimates of costs, outcomes, and cost-effectiveness will be reported as means with 95% confidence intervals. In accordance with the current threshold used in the U.S., prophylactic NPWT will be considered cost-effective if the incremental cost per QALY is less than $100,000[62]. We will conduct sensitivity analysis to evaluate uncertainty of the results by varying probability (e.g., baseline rate of SSI, magnitude of risk reduction) and cost parameters (e.g., cost of the NPWT device, healthcare cost). We will employ Monte Carlo simulation to assess the robustness of our findings by simultaneously sampling distributions of multiple parameters within the model.

Etiology, timing, and risk factors of SSIs in obese women

For these analyses, the two study groups (NPWT and standard care) will be combined into a cohort, and all analyses will adjust for group assignment and study site. We will evaluate wound culture data to determine the types and frequency of different bacteria including MRSA. We will use time-to-event analyses to estimate median time to SSIs and time to heal. We will identify risk factors

for SSI initially based on factors associated with SSI in bivariate analysis (at $P<0.1$ threshold), biological plausibility, and factors reported in the literature[2,63-68]. We will use backwards elimination to reduce the number of variables in the model. Variables that are significant will be retained as risk factors for SSIs in obese women. Fit for the final model will be assessed by using the Hosmer-Lemeshow goodness-of-fit test[69].

Other planned secondary analysis

- Effect of prophylactic negative pressure wound therapy on a composite of any wound complication
- Effect of prophylactic negative pressure wound therapy on rate and type of wound cultures
- Effect of prophylactic negative pressure wound therapy on healthcare resource utilization
- Association between levels of cefazolin in the subcutaneous layer before fascial incision and after fascial closure and risk of surgical site infection
- Risk of surgical site infection and other wound complications with different skin incision types
- Relationship between skin microbiome at the incision site and risk of surgical site infection
- Subcuticular suture type and risk of surgical site infection
- Timing of removal of standard dressing and surgical site infection

7. Safety monitoring

The interventions compared in this trial are both currently used in clinical obstetric practice. Further, the adverse events reported with use of prophylactic NPWT at cesarean were minor and their frequency was comparable to rates with standard dressing[51]. Therefore, no serious or life-threatening adverse events are expected in this trial. Nonetheless, the following measures will be taken to monitor and investigate adverse events:

7.1. Independent Data and Safety Monitoring Board (DSMB)

An independent study-specific DSMB will be composed of three distinguished individuals (Sindhu Srinivas, MD, MSCE; Alison Cahill, MD, MSCI; and Jenifer Allsworth, PhD) who represent appropriate expertise in epidemiology, obstetrics, clinical trials, and biostatistics. They will provide oversight to assure that the trial accrues at a sufficient rate and that the safety and privacy of all study participants is assured. The DSMB will hold conference calls every six months to review study progress and monitor adverse events.

7.2. Adverse events reporting

Reportable Events

Each site-PI will oversee the safety of the study at his/her site. During the study, the investigator or study site personnel will be responsible for querying and recording adverse events (AEs) and serious adverse events (SAEs), as detailed below.

Types of Reportable Events:

Serious Adverse Events (SAE)

The site must report all SAEs to the lead site, whether or not they result from study participation, within 24 hours of learning of the event. A serious adverse event (SAE) is any adverse event occurring within the timelines specified in the protocol that results in any of the following outcomes:

- Death
- Life-threatening situations (subject is at immediate risk of death)
    - Postpartum hysterectomy for infection control
    - Maternal sepsis
    - Necrotizing fasciitis
    - Maternal ICU admission

Adverse Events (AE)

An adverse event is any untoward medical occurrence in a clinical investigation subject administered an investigational product and which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

For this study, abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g., electrocardiogram, X-rays, vital signs) per se are not reported as AEs. Only the Adverse Events of Special Interest (AESI) defined below will be recorded on the CRFs and in the subject's chart.

Adverse Events of Specific Interest (AESI)

Adverse events of particular clinical importance (other than SAEs mentioned above) will be classified as adverse events of specific interest (AESIs). For this study, AESIs refer to:

- Mild/moderate reactions:
    - Skin blisters
    - Wound bleeding
    - Allergic skin reaction

Assessing and Documenting Reportable Events:

Subjects will be evaluated for adverse events in the following manner:

- Routine monitoring by physicians, nurses and research team during inpatient stay, with data obtained from the subject's EMR by research staff.
- Typically patients will be scheduled for routine follow-up with their provider at 1-2 weeks and 4-6 weeks postpartum
- Research staff will call subjects on postoperative day 30 (±2 days) and will ask patients standardized questions regarding wound complications. Medical records will be obtained for any patient or provider-reported complications.

An adverse event report will be generated for each event that will include the following:

- Date of event discovery
- Severity (mild, moderate, severe, life threatening/disabling, death)
- Relationship to treatment
- Action taken
- Outcome
- Expected or unexpected
- Date reported
- Relevant notes/chart records/supporting documentation to corroborate the event
- To whom event was reported (IRB, Sponsor)

- **Non-Severe AESI will be reported to the lead site as aggregate every 6 months, and to the IRB at renewal.**
- **SAEs will be reported within 24 hours of discovery to the IRB and the lead site.**

Relationship of Reportable Events:

An Investigator must make the determination of relationship to the drug for each SAE and/or AESI. The relationship to the drug or device should be assessed using the guidelines presented in the table below.

Relationship to Device	**Description**
Related	● Previously known harmfulness of device; *or* ● Follows a reasonable temporal sequence from administration of the device; *or* ● Follows a known or expected response pattern to the suspected intervention; *or* ● Is confirmed by stopping or discontinuing the device; *and* ● That is not explained by any other reasonable hypothesis
Probably related	• Follows a reasonable temporal sequence from the time of study intervention; *and/or* • Follows a known response pattern to the study device; *and* • Was unlikely to have been produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy
Possibly related	• Follows a reasonable temporal sequence from the time of study intervention; *and/or* • Follows a known response pattern to the study device; *but* • Could have been produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy
Unlikely related	• Does not follow a reasonable temporal sequence from the time of study intervention; *and* • Was likely produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy but for which relationship cannot be definitely ruled out
Not related	The adverse event can be determined with certainty to have no relationship to the study device

Severity of Reportable Events:

The investigator will assess the severity of the AE using the following general guidelines:

Severity	**Description**
Mild:	An AE that is usually transient, requiring no special treatment, and does not interfere with the subject's daily activities.
Moderate:	An AE that introduces a low level of inconvenience or concern to the subject and may interfere with daily activities but is usually ameliorated by simple therapeutic measures.
Severe:	An AE that interrupts a subject's usually daily activity and typically requires systemic drug therapy or other treatment (a severe AE may not necessarily qualify as an SAE).
Life-threatening:	An AE that put the subject at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.

Outcomes of Reportable Events:

The investigator will categorize the outcome of each reportable event according to the definitions below:

Status	**Description**
Resolved:	The subject recovered from the SAE or AESI.
Resolved with sequelae:	A condition whereby the consequences of a disease or injury include lingering effects.
Ongoing:	At the time of the last assessment, the event is ongoing, with an undetermined outcome. Note: Ongoing SAEs and AESIs are not considered resolved as a result of death and no SAE or AESI stop date should be recorded for an AESI that is ongoing at the time of death.
Fatal:	Adverse Event directly caused death. If a subject dies during participation in the study the lead site should be provided with a copy of any post-mortem findings. Note: Death is an outcome of an adverse event and not an adverse event in itself. All reports of subject death should include an adverse event term (other than “Death”) for the cause of the death.

Data Monitoring and Quality Control

Periodic monitoring visits will be made at the investigational site throughout the clinical study to ensure that the investigator obligations are fulfilled, and all applicable regulations and guidelines are being followed. These visits will ensure that the facilities remain acceptable, the investigational plan is being followed, the IRB and local authorities have been notified of approved investigational plan changes as required, complete records are being maintained, appropriate and timely reports have been made to the sponsor and/or its designees and the IRB, and the investigator is carrying out all agreed upon activities.

An annual report will be generated beginning one year after the first enrollment and will include the following:

- A list and summary of adverse events;
- Whether adverse event rates are consistent with pre-study assumptions;
- A summary of recruitment and retention and reason for dropouts;
- Whether the study is on track to be completed and accomplish the stated aims.

Confidentiality:

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

In the event that a subject revokes authorization to collect or use PHI, the investigators, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Data Collection and Management

Case Report Forms—

Qualified study staff at the investigational site will perform primary data collection. Electronic case report forms (eCRFs) will be used to collect all subject data during the study. The investigator is responsible for the accuracy and completeness of all data on the eCRFs. Lead site personnel will review completed eCRFs at regular intervals throughout the study.

Information on the eCRFs will be compared to information originally recorded on source documents related to the study. Information on the eCRF must match the same information on the source documents or a data query will be issued. All eCRFs will be reviewed for completeness, validity, and consistency. Queries will be generated and resolved with the sites and all protocol deviations will be recorded on the eCRF.

Source data—

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic

negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

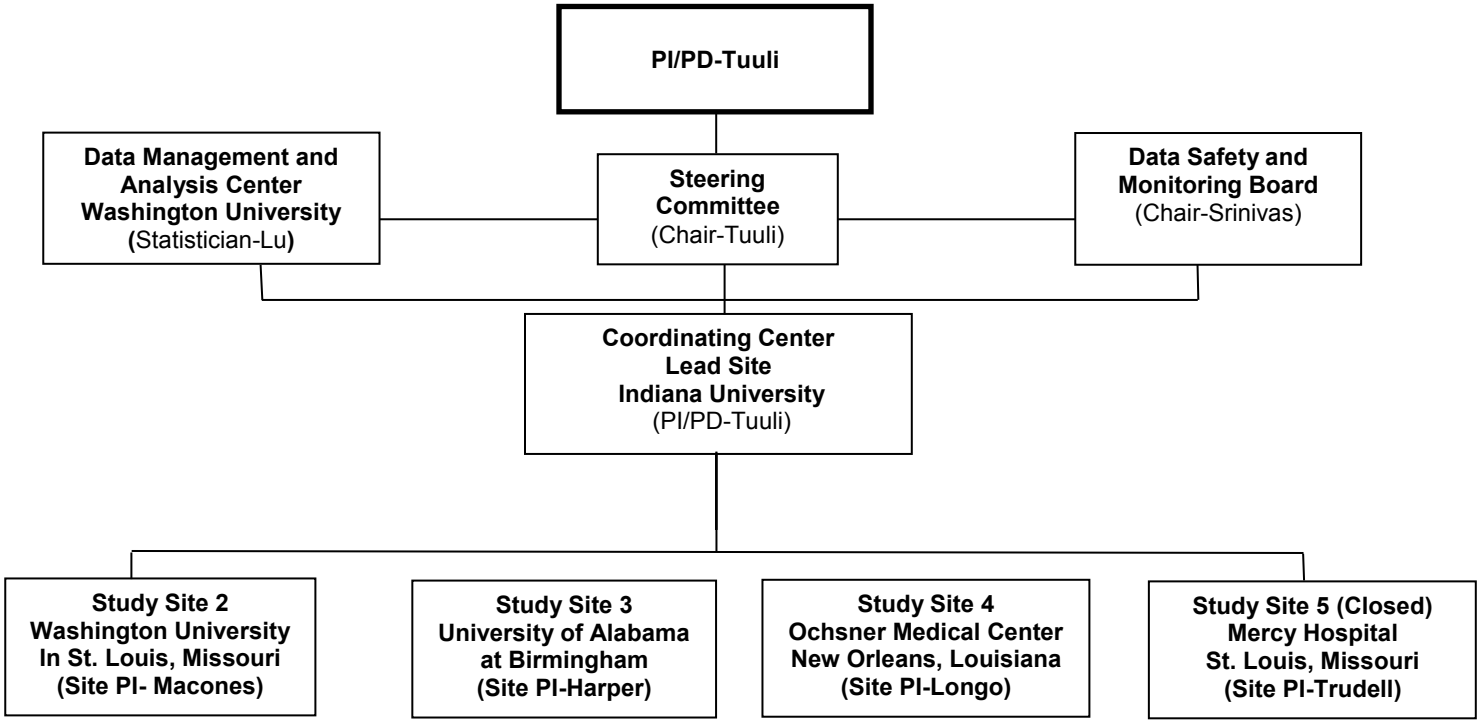
7.3. Interim analyses

We anticipate two interim analyses after 50% and 75% of the sample size are recruited, but the exact timing will be at the discretion of the DSMB. Analyses will be performed by the study statistician and presented to the DSMB, which will make recommendations regarding further conduct of the trial. At their first meeting, the DSMB will establish thresholds and rules for trial stoppage based on safety and efficacy limits. Although early stopping decisions cannot be based purely on a mathematical stopping rule, we will use the Haybittle-Peto stopping rule as a guide[70,71]. Under this rule, the interim analyses of the primary outcome would have to demonstrate an extreme difference between groups ($P < 0.001$) to justify stopping early for efficacy. This rule has the advantages that the exact number of interim analyses need not be specified in advance and the overall type I error is preserved at 0.05; therefore, sample size adjustment for multiple testing is not needed.

8. Study Administration

As a multicenter trial with experienced collaborating investigators, governance will be shared rather than directed by a highly centralized and hierarchal structure. The Coordinating Center will be located at Indiana University and the Data Management Center will be located at Washington University in St Louis. All the investigators will form the Steering Committee, chaired by the PI**.**

Figure 4: Trial administrative structure



Coordinating Center/Lead Site, Indiana University, will be responsible for:

- Maintaining the study protocol and making revisions
- Updating the site operations manual as needed
- Performing overall management and coordination of the intervention and measurements
- Ensuring all Institutional Review Board requirements are up to date at all sites
- Over-seeing and assisting with recruitment
- Providing training and support for data instruments and quality assurance and control

- Coordinating progress reports to the data management center at WashU

The Data Management and Analysis Center, WashU, will be responsible for:

- Creation of randomization sequence
- Creation of the database and extraction tools
- Data cleaning, outlier detection, and preparation for analysis
- Primary analyses of interim data
- Additional analyses as requested by the DSMB or Coordinating Center
- Primary intention-to-treat analyses
- Planned secondary analyses

Participating Clinical Sites will be responsible for:

- Screening and recruiting participants
- Determining participant eligibility
- Designating group assignment as specified by central randomization
- Data entry
- Developing site-internal procedures and training/certifying staff members as appropriate
- Assuring compliance with Institutional Review Board requirements
- Responding to Quality Assurance reports
- Maintaining good recruitment rate
- Reviewing and reconciling study data
- Entering participant data into study database and responding to data cleaning requests
- Submitting inquiries on procedural issues to the Coordinating Center
- Responding to requests for data regarding interim and final analyses and data safety

Steering Committee

The Steering Committee (SC) for the trial will be chaired by The PI. The SC will comprise the PI (Dr Tuuli) and the site-PIs (Drs. Macones, Warren, Harper, and Longo) and Health Economist Co-I (Dr Caughey). The functions and responsibilities of the SC are:

- Decision making regarding participant eligibility and study end points
- Publication and presentation guidelines
- Authorship determination
- Consideration and approval of ancillary studies
- Addressing scientific or operational matters as they arise

The investigators are all experienced and most have collaborated in prior studies. Any issues will be addressed at regular Steering Committee conference calls and yearly scheduled meetings to coincide with the annual Society for Maternal Fetal Medicine meeting attended by most investigators.

Data Safety and Monitoring Board (DSMB)

A DSMB has been established to ensure objective oversight of the trial's safety and conduct. Members of the Data Safety and Monitoring Board will be Sindhu Srinivas, MD, MSCE (Chair); Alison Cahill, MD, MSCI; and Jenifer Allsworth, PhD, who represent appropriate expertise including epidemiology, infectious disease, obstetrics, clinical trials, and biostatistics. Members are not involved in any aspect of the trial operation. They will provide oversight to assure that the trial accrues at a sufficient rate and that the safety and privacy of all study participants is assured. The DSMB will hold conference calls every six months to review study progress and monitor adverse events. The DSMB will be confidentially briefed by the study statistician before each meeting regarding study progress, and study outcomes. That information will be available to the study investigators once disclosed by the DSMB. The DSMB will issue a written report to the investigators after each meeting outlining any study issues and needed actions.

9. Protection of Human Subjects

Assessment of Risks

Subject Characteristics

All women admitted to the labor and delivery units of the participating medical centers will be screened against inclusion and exclusion criteria. Eligible subjects will be approached for written consent to participate in the study. Consent forms will be translated and back translated (primarily into Spanish, but others as necessary) for non-English speaking participants. The informed consent process for these participants will be conducted by an interpreter with the research staff present, or by research staff fluent in the subject's native language. Consented subjects will be randomized once they are committed to cesarean delivery. We will use broad inclusion criteria to ensure generalizability of our results.

Table 5: Inclusion and exclusion criteria

Inclusion criteria (rationale)
• Gestational age ≥23 weeks (gestational age at which cesarean deliveries are typically performed) • Prepregnancy BMI≥30 (Based on BMI at first prenatal visit; group of women at particularly high risk for both cesarean delivery and SSIs) • Planned or unplanned cesarean delivery (procedure in which NPWT is being tested)
Exclusion criteria (rationale)

• Unwillingness or unable to consent
• Non-availability for postoperative follow-up (follow-up is needed to ascertain study outcomes)
• Contraindication to NPWT applicable to women undergoing cesarean (device will not be used in patients with contraindications)
  ○ Pre-existing infection around incision site
  ○ Bleeding disorder
  ○ Therapeutic anticoagulation
  ○ Prior irradiated skin
  ○ Allergy to any component of the dressing (e.g. silicone, silver, adhesive tape)

Potential Risks

The potential risk to study subjects is expected to be minimal, but include the following:

1. Loss of confidential health information.
2. Skin blisters, allergic skin reactions, or wound bleeding.

Adequacy of protection against risks

Protection of Confidentiality

Consent from patients will be obtained in a private setting, such as a quiet conference area or the patient's private room. Data will be collected and managed with *REDCap* (Research Electronic Data Capture), an established, secure, web-based data capture and management tool developed at Vanderbilt University and supported by the bioinformatics team at Washington University School of Medicine (http://www.biostat.wustl.edu/redcap/). The REDCap application executes within the private zone of the WUBIOS Computing Resource within the Division of Biostatistics. This private zone is separated from the Internet and the general WUSTL network by a firewall. WUBIOS is a professionally managed, HIPAA compliant network which has been approved by the WUSM security officer. Access to REDCap is restricted to either computers which are located within WUBIOS or other WUSM secure networks or which have a WUBIOS issued digital certificate installed in the user's browser. Users of REDCap are required to sign a user agreement and be authorized by their supervisor. A user specific userID/password is required for logging into REDCap. For each research project, IRB approval is required and an administrator within the project grants specific users access rights to the project. Read or Read/Edit privileges are granted on a form-by-form basis for each user. Rights to download data are also controlled by the project administrator.

As the data are entered into the electronic database, the database will be password protected. Only research staff of this project will have authorization to access the files, with permission controlled by the Data Manager; all other access will be prohibited. Access to the files will be logged electronically, and access will only be made for the purposes of conducting the study.

All data collected for this study will be used for research purposes only. The data collected from the medical record will be limited to only what is necessary to carry out the study as outlined. No data from the study will be reported on an individual basis; all findings from this study will be reported in statistical summary form only. All members of the research team will treat all data with strict confidentiality. Each subject will be assigned a unique study code number that will be used on all data forms; patient names will not be abstracted. A list of patient names and study code numbers will be maintained separately from the data extraction forms, securely. Only the investigators and project staff, with the proper training on research practices including the protection of confidentiality, will have access to this information. The data extraction forms will also be kept in the aforementioned secure fashion, and only research team members will be granted access.

Potential Benefits/Importance of knowledge gained

The study is not designed to provide direct benefits to research participants. Nonetheless, if our hypothesis that obese women will have lower rates of SSIs after cesarean with use of prophylactic NPWT than with standard care is correct, then subjects randomized to NPWT will have the benefits lower rates of SSIs. More importantly, results from this study have the potential to improve outcomes for obese women undergoing cesarean delivery. Because the anticipated risk to participants is minimal, the risks-benefit ratio is very favorable.

10. Study Time Table

The schedule of key activities over the 5-year project period is depicted in **Table 5** below.

Table 5: Study Timeline

Project Period (months)	**0-6**	**6-12**	**12-18**	**18-24**	**24-30**	**36-42**	**42-48**	**48-54**	**54-60**
Protocol development & IRB									
Staff recruitment and training									
Study forms and database									
Subject recruitment									
Data collection & management									
Data analysis									
Drafting of manuscript & reports									

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